EXPLORING NEW GOLD-CATALYZED CYCLIZATION REACTIONS OF 1,5-ENYNES AND DEVELOPMENT OF AN INTERMOLECULAR PHENOL SYNTHESIS

Nuria Huguet i Subiela

Dipòsit Legal: T.449-2013

Núria Huguet i Subiela

Exploring New Gold-Catalyzed Cyclization Reactions of 1,5-Enynes and Development of an Intermolecular Phenol Synthesis

DOCTORAL THESIS

supervised by Prof. Antonio M. Echavarren

Institut Català d'Investigació Química (ICIQ)

Institut Català d'Investigació Química

Universitat Rovira i Virgili

Tarragona 2013

Institut
Català
d'Investigació
Química

Av. Països Catalans, 16
43007 Tarragona
Tel. 977 920 218
Fax. 977 920 255

FAIG CONSTAR que aquest treball, titulat "Exploring New Gold-Catalyzed Cyclization Reactions of 1,5-Enynes and Development of an Intermolecular Phenol Synthesis", que presenta Núria Huguet i Subiela per a l'obtenció del títol de Doctor, ha estat realitzat sota la meva direcció al Institut Català d'Investigació Química vinculat a la Universitat Rovira i Virgili i que acompleix els requeriments per poder optar a Menció Internacional.

Tarragona, Març de 2013

El Director de la Tesi Doctoral

Prof. Antonio M. Echavarren

Als meus pares

"Para mí, no hay emoción comparable a la que produce la actividad creadora, tanto en ciencia como en arte, literatura u otras ocupaciones del intelecto humano. Mi mensaje, dirigido sobre todo a la juventud, es que si sienten inclinación por la ciencia, la sigan, pues no dejará de proporcionarles satisfacciones inigualables. Cierto es que abundan los momentos de desaliento y frustración, pero estos se olvidan pronto, mientras que las satisfacciones no se olvidan jamás"

Severo Ochoa

Aquest treball de Tesi Doctoral s'ha realitzat a l'Institut Català d'Investigació Química (ICIQ) a Tarragona (Octubre 2008-Octubre 2012) baix la direcció del Professor Antonio M. Echavarren, a qui li vull agrair tota la seva dedicació, temps i confiança depositada amb mi i per haver-me donat tantes oportunitats al món de la investigació.

El treball recollit a aquesta memòria s'ha dut a terme gràcies al finançament de l'Institut Català d'Investigació Química (Octubre-Desembre 2008), una beca de Formació de Personal Investigador de l'Agència de Gestió d'Ajuts Universitaris i de Recerca (Gener-Juny 2009)), i una beca de Formació de Professorat Universitari del Ministeri d'Educació i Ciència (Juliol 2009-Setembre 2012).

Durant aquest període he realitzat una estada breu al grup d'investigació del Professor Tobias Ritter (Harvard University, Cambridge, EEUU, Setembre-Desembre 2011) a qui agraeix tota la seva dedicació i disposició, i sobre tot la seva motivació i ajuda en tot moment. També he tingut la oportunitat de realitzar una estada a BASF SE (Ludwigshafen, Alemanya, Novembre 2012-Febrer 2013) baix la supervisió del Dr. Marek Pazicky al qui li agreix l'oportunitat de poder formar part del seu grup.

Voldria agrair tot el suport de Sònia Gavaldà, Vanessa Martínez i Imma Escofet tant per la seva dedicació fent el treball més fàcil com pel suport personal. Gràcies!

M'agradaria expressar el meu agraïment al servei d'espectrometria de masses; al servei de RMN; al servei de Ray-X i al servei de tecnologia informàtica, sen se la vostra ajuda aquest treball podria haver-se allargat molt més

A tot el grup Echavarren: Claudia de León, Dr. Paul McGonigal: thanks for being such a great person and chemist!! Madeleine Livendahl, mi sueca a la que tanto he echado de menos este último año, Dra. Lorena Riesgo, Anna Ohms, Carla Obradors, Anthony Pitaval, Morgan Gaydou, the Gentleman: Yahui Wang, Dr. David Lebouf, Dra. Ricarda Miller, Masha Kirillova, Katya Smirnova, Ruth Dorel i Pili Calleja. I als que ja no

estan al grup i que tant em disfrutat i compartit: Dra. Ana Escribano, Dr. Dominic Janssen, Dr. Kian Molawi, Dra. Elena Herrero-Gómez, Dra. Paula de Mendoza, Dr. Ricardo Sinisi, Dr. Jose María Blasco, Dra. Nolwenn Martin, Dr. Julien Ceccon, Dr. Mihai Raducan, Dra. Patricia Pérez-Galán, Dra. Verónica López-Carrillo... THANKS!!!

La veritat es que aquest quatre anys de tesis no haguessin estat el mateix si no fora pels bons moments i el suport dels meus amics. Gràcies per formar part de la meva experiència, i estar aquí en tot moment. Us estime i estareu amb mi sempre: Sara, Mireia, Esther, Gloria, Anna, Amaia, Núria, Begoña, Joana, Vero, Mónica, Cristina i Iris, unides per un vincle que es la dansa. Gràcies per formar part de la meva experiència, i estar aquí en tot moment. Us estime i estareu sempre amb mi. A las que empezasteis esta nueva etapa de mi vida conmigo: Helen y Nina, siempre quedará la summerfellow!!! Als meus primers companys de pis Nora i Toni; i com no a tu Isa, veïna i gran amiga. A mis compañeros de master: Carlo, Moira, Isi, Mercé, Miriam, Cristina i Oriol, juntos empezamos de algún modo esta experiencia y la vamos acabando como Doctores. Especial agracimiento para Jose y Judit. A la gente que durante parte de estos años compartió batallas conmigo: Laura, Jaime, Alba, Helmut y Pablo. Y finalmente, al Dr. Margarito Martínez: "Solo te puedes arrepentir de lo que haces, no de lo dejas de hacer..." A mis Bostonianos, sin vosotros esos 4 meses no hubiesen sido igual: María, Anna, Elena, Laura, Devin, Alex, Sergi, Ramsés, Jesús, Thais, y mis "granadinas" Alba y Tania.
También quiero agradecer a aquellos que crecisteis conmigo y que pese a la distancia ahora más que nunca os considero grandes amigos: Eli, Sonia, María, Vero, Jose, Pablo G. y Laura (más que una prima para mí).

Finalment, el meu més sincer agraïment es per la meva família sobre tot als meus pares. Tot açò no seria possible sen se el vostre suport, dedicació i estima. Gràcies per estar en tot moment al meu costat per tal de poder fer els meus somnis realitat, gràcies per la vostra confiança.

Fins al moment de redactar aquesta memòria, els resultats aquí descrits han donat lloc a les següents publicacions:

Nature of the Intermediates in Gold(I)-Catalyzed Cyclizations of 1,5-Enynes

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

Gold-Catalyzed Cyclization of Oxo-1,5-Enynes

Huguet, N.; Echavarren, A. M.

Synlett **2012**, *23*, 49-53.

Durant aquest anys he escrit els següents capítols de llibres:

Gold-Catalyzed O-H Bond Addition to Unsaturated Organic Molecules

Huguet, N.; Echavarren, A. M.

Topics in Organometallic Chemistry: Hydrofunctionalization, Ed. Springer, **2012**, *43*. DOI: 10.1007/978-3-642-33735-2.

Asymmetric Gold-Catalyzed Reactions

Huguet, N.; Echavarren, A. M.

ASTE-II, Ed. Wiley, **2012**.

Gold–Catalyzed Cyclizations of Alkyne with Alkenes and Arenes

López–Carrillo, V.; Escribano–Cuesta, A.; Huguet, N.; Echavarren, A. M.

Organic Reactions, accepted.

Handbook of Homogeneous Gold Catalysis (Catalytic Science Series)

Huguet, N.; Echavarren, A. M.

Imperial College Press (London), **2012**, submitted.

Agència
de Gestió d'Ajuts
Universitaris
i de Recerca

UNIVERSITAT ROVIRA I VIRGILI

Aquesta memòria de treball de Tesi Doctoral s'ha dividit en sis parts diferents: un resumen en català, una introducció general, que engloba les propietats generals i la reactivitat de l'or, i quatre capítols, en els que es descriu la major part de la investigació que he dut a terme. Al mateix temps cada capítol està dividit en cinc parts: una introducció específica sobre el tema a desenvolupar, un descripció dels objectius proposats, un apartat de resultats i discussions dels mateixos, les conclusions de la investigació realitzada i finalment, una secció amb la part experimental on s'explica com s'ha sintetitzat cada compost junt amb la seva caracterització analítica corresponent.

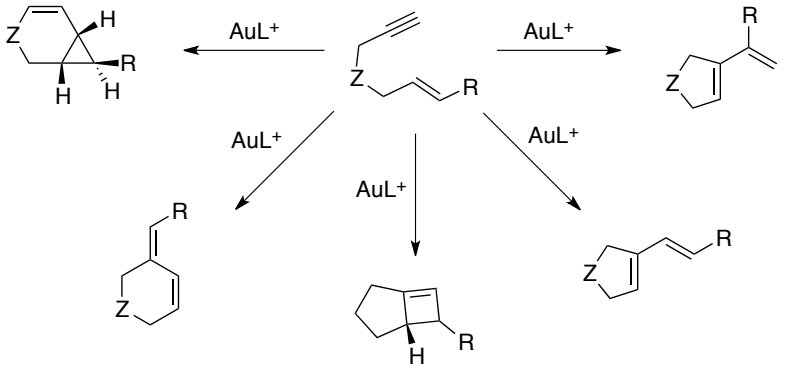
L'apartat *Introduction* descriu els principis bàsics sobre la catàlisi homogènia amb or a l'activació d'alquins, particularment en les cicloisomeritzacions d'enins i els corresponents aspectes mecanístics.

El treball descrit al *Chapter* 1. *Cycloisomerizations of 1,5-Enynes: Towards the Synthesis of Anhydrocannabimovone*, s'ha realitzat en col·laboració amb Ángeles Mosquera, durant una estada de tres mesos, i la doctoranda Verónica López-Carrillo. Alguns dels seus resultats s'han inclòs per assegurar la coherència en el desenvolupament de la discussió. El treball on s'aplica la metodologia desenvolupada a la *Synthesis of Anhycrocannabimovone* no s'han inclòs en aquesta tesis i serà inclòs per Masha Kirillova a la seva tesis.

Una part descrita al *Chapter 2. Gold(I)-Catalyzed Cycloaddition of 1,5-Benzylenynes* sobre la *synthesis of Pycnanthuquinone C* s'ha dut a terme amb la col·laboració del Dr. Paul McGonigal. Aquesta col·laboració s'ha indicat com a peu de nota a l'apartat corresponent.

Resum

Durant els últims anys, el nostre grup de recerca s'ha centrat en el desenvolupament de nous complexos d'or(I) i les seves aplicacions a noves reaccions de ciclacions d'enins, focalitzant-se tan en el desenvolupament de noves metodologies així com en l'estudi del mecanisme pel qual la reacció té lloc. El cas més estudiat és la ciclació d'1,6-enins que dóna lloc a una gran varietat de productes en presència de diferents catalitzadors d'or. La formació d'un producte o un altre està marcada bàsicament per tres factors: el lligand enllaçat al complex d'or, les condicions a les que té lloc la reacció i substrat de partida.

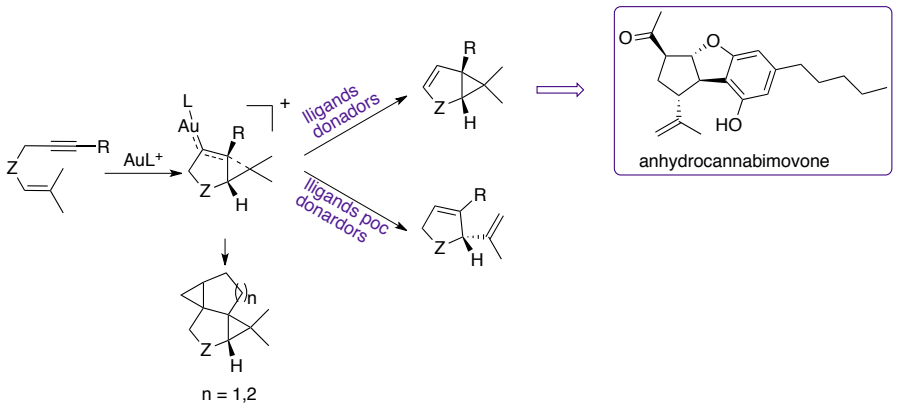


Esquema I

En aquesta Tesis Doctoral s'han estudiat els mecanismes i la reactivitat dels 1,5-enins. A diferència dels 1,6-enins, els quals normalment reaccionen en presència de catalitzadors d'or mitjançant un camí de reacció 6-*exo-dig*, els 1,5-enins normalment reaccionen via ciclacions 5-*endo-dig* a través d'intermedis del tipus ciclopropil carbens d'or. En aquest context, el treball d'aquesta Tesi Doctoral s'ha dividit en tres blocs diferents on s'han estudiat la reactivitat i el mecanisme de diferents 1,5-enins.

El primer capítol d'aquesta Tesi Doctoral està enfocat a l'estudi de la influència que presenten els diferents lligands enllaçats als complexos

d'or en l'evolució de la reacció de ciclació d'1,5-enins simples.[i] Durant aquest estudi, s'ha pogut capturar l'intermedi ciclopropil carbè d'or a través de la ciclopropanació intramolecular que té lloc de forma concertada, d'acord amb càlculs DFT. Aquesta nova metodologia de cicloisomerització d'enins s'està aplicant actualment a la síntesis total de la anhydrocannabimovone,[ii] un cannabinoid sintètic amb interessant activitat biològica.



Esquema II

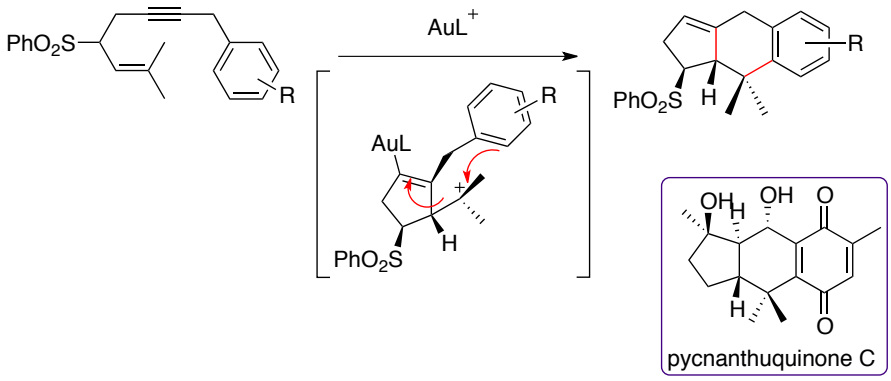
El segon capítol d'aquesta memòria segueix amb la línia d'estudi de ciclacions d'1,5-enins. Concretament s'ha examinat la reacció de cicloaddició d'1,5-benzilenins en presència de diferents catalitzadors d'or(I) formant productes tricíclics amb unes condicions de reacció suaus. El mecanisme de reacció proposat és molt similar a la reacció de cicloaddició [4+2] dels 1,6-arilenins descrita prèviament pel nostre grup de recerca.[iii]

i López-Carrillo, V.; Huguet, N.; Mosquera, A.; Echavarren, A. M. *Chem. Eur. J.* **2011**, *17*, 10972.

ii Taglialatela-Scafati, O.; Pagani, A.; Scala, F.; De Petrocellis, L.; Di Marzo, V.; Grassi, G.; Appendino, G. *Eur. J. Org. Chem.* **2010**, 2067.

iii (a) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269-279. (b) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178-6179.

Aquesta nova metodologia s'ha utilitzat com el pas clau per la síntesi de la pycnanthuquinone C.[iv]

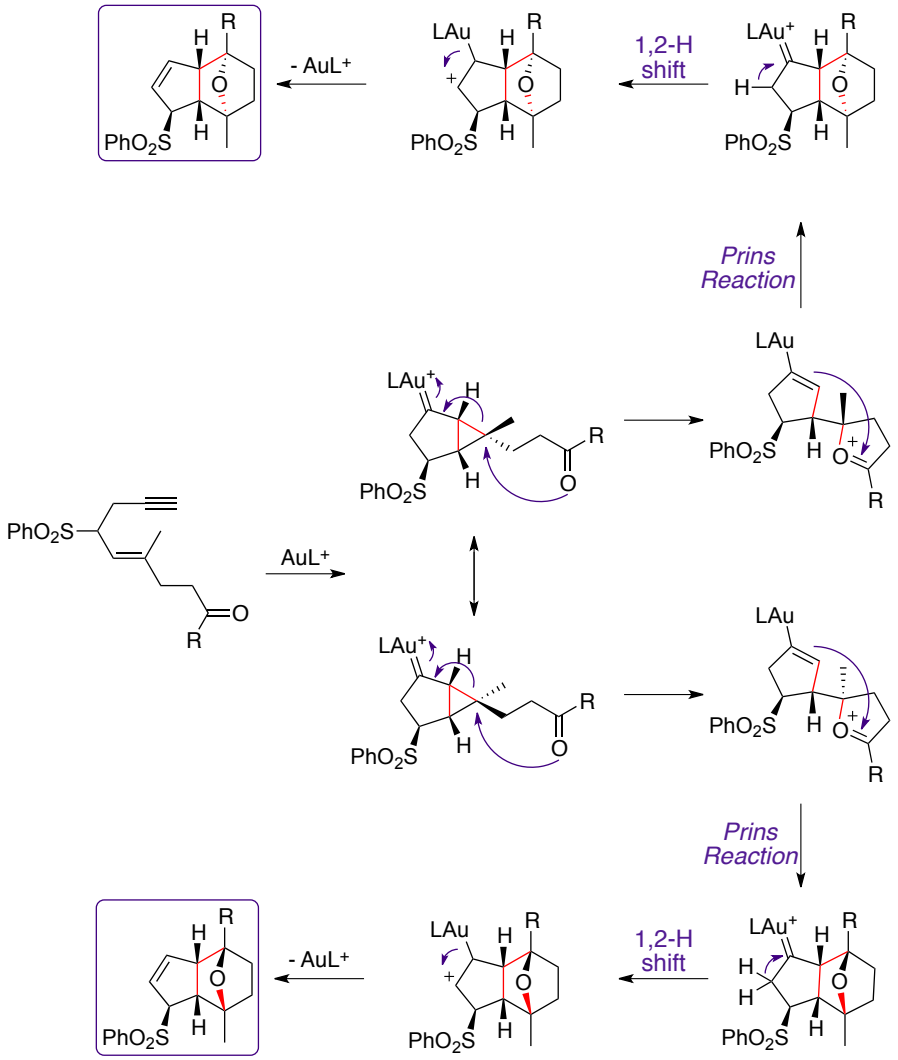


Esquema III

El tercer capítol d'aquesta Tesis Doctoral concentra la reacció intramolecular d'enins amb grups carbonils, és a dir, la cicloaddició [2+2+2] alquè/alquí/carbonil.[v] En aquest cas, la reacció té lloc mitjançant un mecanisme tipus reacció de Prins obtenint productes oxatricíclics (*Esquema IV*). La selectivitat d'aquesta reacció depèn del lligand així com de l'isòmer *E* o *Z* de l'ení de partida. S'han dut a terme càlculs teòrics per tal de determinar el mecanisme de reacció i l'estereoquímica de la mateixa. L'estructura d'aquest productes tricíclics ha estat determinada mitjançant experiments bidimensionals (entre d'ells NOE) i difracció de Raigs X.

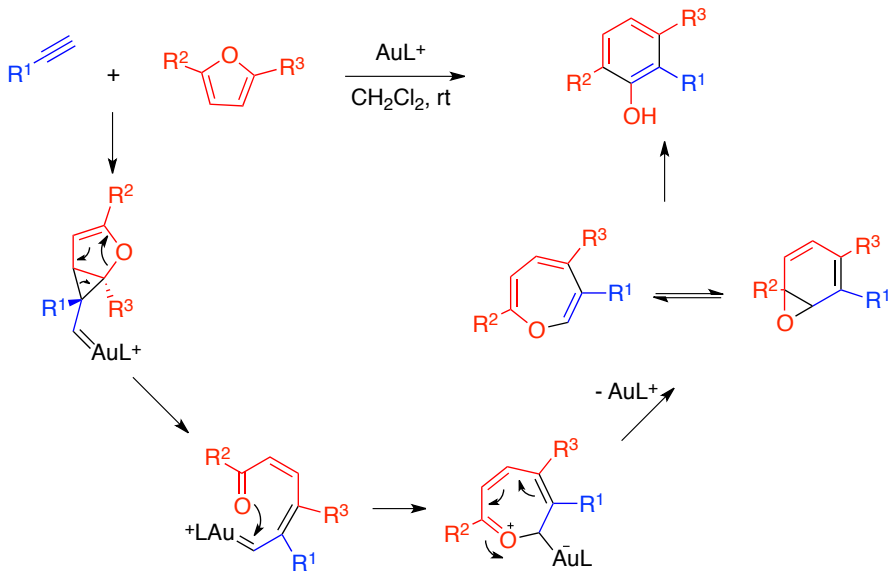
iv Laird, D. W.; Poole, R.; Wikström, M.; van Altena, I. A. *J. Nat. Prod.* **2007**, *70*, 671.

v Huguet, N.; Echavarren, A. M. *Synlett* **2012**, *23*, 49.


- AuL+
1,2-H shift
Prins Reaction
AuL+
Prins Reaction
- AuL+
1,2-H shift

Esquema IV

Finalment, l'últim capítol d'aquesta memòria demostra que la reacció intermolecular entre furans i aquins catalitzada per Au(I) dóna lloc a la formació de fenols quan s'utilitzen lligands donadors com els carbens *N*-heterocíclics (NHC), millorant així el resultat descrit pel grup del Prof. Hashmi.[vi] Mecanísticament es proposa l'atac nucleòfil del furà a l'acetilè (prèviament coordinat a l'or) per formar el ciclopropil carbè d'or.[vii] La ruptura d'un enllaç C-C i d'un enllaç C-O del ciclopropil carbè d'or forma l'intermedi carbonílic que, mitjançant ciclació i eliminació d'or(I) dóna lloc a l'oxapina que està en equilibri amb el epoxiaré. Finalment, l'obertura de l'epòxid dóna lloc a la formació del fenol final.



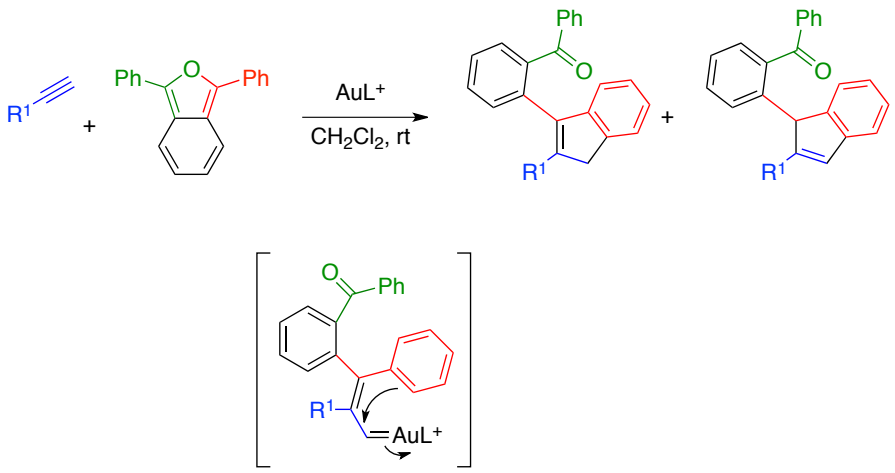
Esquema V

Quan la reacció es duu a terme amb el 1,3-isobenzofurà, s'obtenen indens com a producte final. En aquest cas en comptes de produir-se l'atac

vi Hashmi, A. S.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769.

vii (a) Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.***2003**, *125*, 5757. (b) Martín-Matute, B.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2001**, *40*, 4754-4757.

nucleòfil per part del grup carbonil és l'anell aromàtic qui produeix l'atac al carbè d'or.



Esquema VI

Abbreviations and Acronyms

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

Introduction

Electrophilic activation of alkynes by late transition metals that act as π-Lewis acids triggers a wide variety of synthetically useful transformations.[1,2,3,4,5,6,7] In this context, gold catalysts present new opportunities for chemical synthesis, and it is therefore not surprising that gold complexes have captured the attention of the chemical community due to their high activity and exquisite selectivity.

1 Zhang, L.; Sun J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271-2296.

2 Sohel, S. M. A.; Liu, R.-S. *Chem. Soc. Rev.* **2009**, *38*, 2269-2281.

3 Belmont, P.; Parker, E. *Eur. J. Org. Chem.* **2009**, 6075-6089.

4 Shen, H. C. *Tetrahedron* **2008**, *64*, 7847-7870.

5 Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, 675-691.

6 Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268-4315.

7 (a) Jiménez-Nuñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326-3350. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Comm.* **2007**, 333-346.

Metal-Catalyzed Alkyne Activation

Activation of alkynes, alkenes, carbonyls, and imines by Lewis acids comprise a group of reactions of considerable interest in organic synthesis.[7,8] In the field of transition metal catalysis, alkynes have been particularly important substrates due to their ready introduction in synthetic intermediates.

In the presence of metal salts, alkynes react as basic Lewis donors, donating electrons to the electron deficient metal as π ligands. The strong coordination between the alkyne and the metal can be explained by the Dewar-Chatt-Ducanson model.[9] Both π-orbitals of the alkyne participate in the interaction with the metal center resulting in: (1) a σ-symmetric M←L donation formed by overlap of the π system of the alkyne with an empty orbital of the metal; (2) a π-symmetric M→L back-donation of electron density from a filled metal d orbital into an antibonding π* orbital of the alkyne. A third interaction could take place involving a M←L π donation between the second orthogonal π orbital of the alkyne and an empty d orbital of the metal that results in a σ-donor/π-donor behavior of the alkyne.

8 (a) Hashmi, A. *Gold Bull.* **2003**, *36*, 3-9. (b) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208-3221. (c) Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Comm.* **2009**, 5075-5087.

9 (a) Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1951**, *18*, C71–C79. (b) Chatt, J.; Duncanson, L. A. *J. Chem. Soc.* **1953**, 2939-2947.

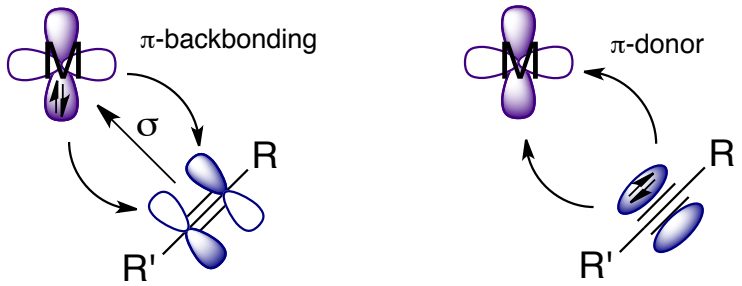


Figure 1. Orbital interaction in metal-alkyne complexes.

The Dewar-Chatt-Ducanson model predicts an elongation of the triple bond by transfer of electron density into the antibonding π* orbital, resulting in rehybridization. Consequently, the alkyne becomes more electrophilic and is susceptible of nuclophilic attack on the unsaturated C-C bond. A well-known example in which this interaction occurs is the addition of water to alkynes catalyzed by metal salts. The metal-mediated hydration of an alkyne was discovered using mercury(II) bromide[10] to produce acetaldehyde. This reaction has been extensively applied in synthesis, although due to the toxicity of mercury compounds and the relatively low turnover numbers (<500) much effort has been made to find new catalysts. Thus, transition-metal complexes containing Pd(II),[11] Pt(II),[12] Ru(II),[13] Rh(III),[14] and other metal centers have been used, although in most cases the catalytic efficiency was only moderate. The first hydration in the presence of gold was studied in 1976 using $HAuCl_4$ as catalyst.[15a] Further

10 Kutscheroff, M. *Chem. Ber.* **1881**, *14*, 1540-1542.

11 Harman, W. D.; Dobson, J. C.; Taube, H. *J. Am. Chem. Soc.* **1989**, *111,* 3061-3062.

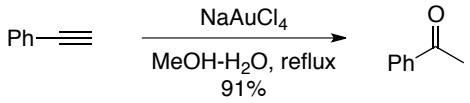
12 Hiscox, W.; Jennings, P. W. *Organometallics* **1990**, *9*, 1997-1999.

13 Tokunaga, M.; Wakatsuki, Y. *Angew. Chem. Int. Ed.* **1998**, *37*, 2867-2869.

14 James, B. R.; Rempel, G. L. *J. Am. Chem. Soc.* **1969**, *91*, 863-865.

15 (a) Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. So.c Perkin Trans. 1,* **1976,** 1983. (b) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729-3731. (c) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418. (d) Scheneider, S. K.; Herrmann, W. A.; Herdtweck, E. *Z. Anorg. Allg. Chem.* **2003**, *629*, 2363-2370.

modifications using $NaAuCl_4$ as catalyst,[14b] cationic gold(I) complexes of the general type AuL^+ (where L is a phosphine, a phosphite, or an arsine)[14c] or gold(I) carbene complexes with a gold-oxygen bond [Au(R^2-imy)OC(O)CH_3][14d] were later reported.



Scheme 1. Hydration of alkynes catalyzed by $NaAuCl_4$.

Properties of Gold

Gold, "the precious metal", is probably one of the few chemical elements that everyone has heard of. Metallic gold is central in the Greek myth of King Midas or in the monetary system, as well as in medicine due to its high biocompatibility. However, gold is toxic in its ionic forms. It is a rare element although it is more abundant than palladium, ruthenium, or iridium. Its unusual stability associated high value, led to organic chemists largely neglecting gold for many years.[16]

In the presence of organic substrates, three different oxidation states are possible: gold (0), gold (I) and gold (III). From a catalytic point of view, the soft[17] character and the polarizability of the gold (I) cation allows performing organic transformations under mild conditions. An important property is its high electronegativity[18] as a result of the relativistic contraction of the valence 6s and 6p orbitals, imparting its high Lewis acidity. This relativistic effect reaches a maximum in gold.[8b]

16 (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180-3211. (b) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239-3265.

17 Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533-3539.

18 (a) Pyykkö, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 3573-3578. (b) Pyykkö, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4412-4456. (c) Pyykkö, P. *Inorg. Chim. Acta* **2005**, *358*, 4113-4130. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395-403.

Gold Complexes for Alkyne Activation

Gold salts and complexes are the most active catalysts known for the electrophilic activation of alkynes under homogeneous conditions. Two different modes of activation have been observed (*Scheme 2*): (1) activation of alkynes via π-complexation promoting the nucleophilic attack to form *trans*-alkenyl-gold complexes as intermediates;[1,8b,19] (2) formation of gold σ-acetylide complexes due to exchange with the acidic terminal proton of the alkyne.[8a, 20] A number of alkyne-gold complexes have been characterized[20a, 21] and studied in solution.[22] In addition, dual σ,π-activation[20,23] of alkynes has been observed (*Scheme 2* (3)). For molecules bearing two alkynes (one internal and one terminal alkyne) dual activation occurs in a different way: σ-activation of the terminal alkyne and

19 (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813-834. (b) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, 215-236. (c) García-Mota, M.; Cabello, N.; Maseras, F.; Echavarren, A. M.; Pérez-Ramírez, J.; Lopez, N. Chem. Phys. Chem. **2008**, *9*, 1624-1629. (d) Hashmi, A. S. K.; Toste, F. D. *Modern Gold Catalyzed Synthesis*; Wiley, **2012**. (e) Pernpointner, M.; Hashmi, A. S. K. *J. Chem. Theory Comput.* **2009**, *5*, 2717-2725.

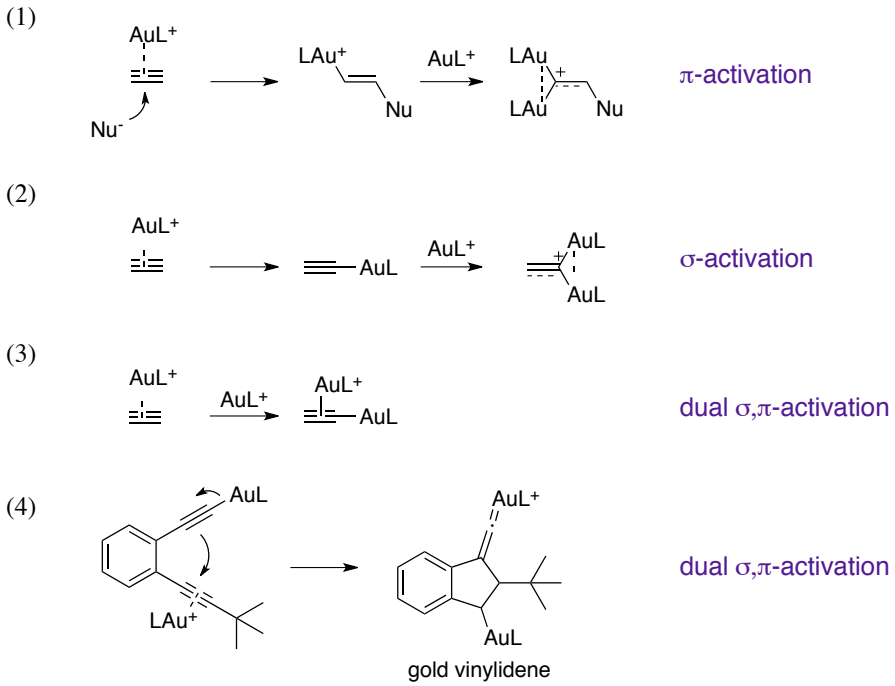
20 (a) Brown, T. J.; Widenhoefer, R. A. *Organometallics* **2011**, *30*, 6003-6009. (b) Gómez-Suárez, A.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2012**, *51*, 8156-8159. (c) Hooper, T. N.; Green, M.; Russell, C. A. *Chem. Comm.* **2010**, *46*, 2313-2315. (d) Blanco, M. C.; Cámara, J.; Gimeno, M. C.; Jones, P. G.; Laguna, A.; López-de-Luzuriaga, J. M.; Olmos, M. E.; Villacampa, M. D. *Organometallics* **2011**, *31*, 2597-2605.

21 (a) Akana, J. A.; Bhattacharyya, K. X.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 7736-7737. (b) Flügge, S.; Anoop, A.; Goddard, R.; Thiel, W.; Fürstner, A. *Chem. Eur. J.* **2009**, *15*, 8558-8565.

22 (a) Zuccaccia, D.; Belpassi, L.; Rocchigiani, L.; Tarantelli, F.; Macchioni, A. *Inorg. Chem.*, **2010**, *49*, 3080-3082. (b) Huettel, R.; Forkl, H. *Chem. Ber.* **1972**, *105*, 1664-1673.

23 Grirrane, A.; Garcia, H.; Corma, A.; Álvarez, E. *ACS Catalysis* **2011**, *1*, 1647-1653.

π-activation of the internal alkyne.[24] This type of intermediate can evolve to form gold vinylidenes



Scheme 2. Activation of alkynes by gold complexes.

Gold-catalyzed transformations involving terminal alkynes may involve the formation of *gem*-σ,σ-diaurated species (*Scheme 2* (1) and (2)).[25]

24 (a) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 4456-4460. (b) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Nösel, P.; Jongbloed, L.; Rudolph, M.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 555-562. (c) Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *134*, 31-34. (d) Hashmi, A. S. K.; Braun, I.; Rudolph, M.; Rominger, F. *Organometallics* **2012**, *31*, 644-661. (e) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Rudolph, M.; Rominger, F. *Angew. Chem. Int. Ed.* **2012**. *51*, 10633-10637.

Recently, σ,π-diaurated intermediates have been verified as an alternative binding mode for digold-vinyl intermediates.[26]

Commercially available AuCl, $AuCl_3$ and $NaAuCl_4$ are sufficiently alkynophilic to catalyze reactions with alkynes. It is important to note that gold(III) may be reduced to gold(I) by oxidizable substrates.[27] The reactivity of gold(I) complexes can be tuned by using different ligands as well. Thus, an increase in the electron-density of the metal is clearly observed by moving from gold(I) complexes with electron-withdrawing to electron-donating ligands.

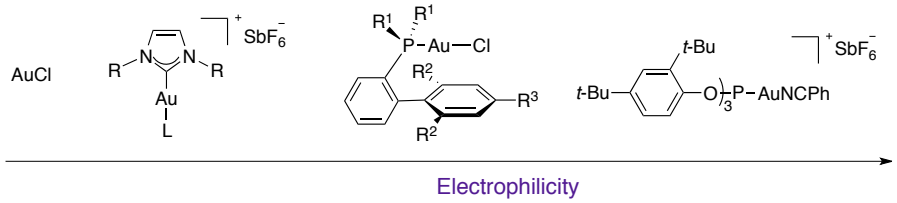


Figure 2. Ligand modulation of the reactivity of gold(I) complexes.

Gold(I) exhibits a strong preference to form two-coordinate linear complexes. As a consequence, it is necessary to abstract one ligand from neutral gold species of the type LAuX to induce sufficient reactivity by the *in situ* generation of the cationic complexes $LAuS^+$. Thus, cationic gold(I) complexes can be prepared by chloride abstraction with different silver salts in the presence of weakly coordinating ligands such as acetonitrile or

25 (a) Weber, D.; Tarselli, M. A.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 5733-5736. (b) Seidel, G.; Lehmann, C. W.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 8466-8470. (c) Brown, T. J.; Weber, D.; Gagné, M. R.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2012**, *134*, 9134-9137. (d) Hashmi, A. S. K.; Braun, I.; Rudolph, M.; Rominger, F. *Organometallics* **2012**, *31*, 644-661.

26 Weber, D.; Gagné, M. R. *Chem. Sci.* **2013**, *4*, 335-338.

27 Morita, N.; Krause, N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1897-1899.

benzonitrile.[28] This is the case for gold(I) halide complexes **A-D** (*Figure 3*) with bulky biaryl phosphines, one of the most commonly used classes of gold complexes.[29]

Cationic complexes **G-J**[30] have been shown to be more convenient catalysts in the cycloisomerizations of enynes and related transformations as they are highly active yet stable to ambient laboratory conditions.[28b,31] Similar complexes **E** and **F** with a weakly coordinated bis(trifluoromethanesulfonyl)amide group (NTf_2, Tf = CF_3SO_2) have also been reported.[32]

28 (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406. (b) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1694-1702. (c) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306-6316.

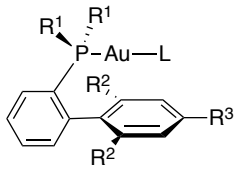
29 Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178-6179.

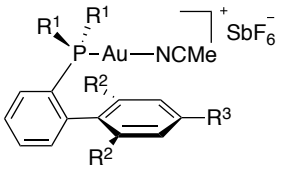
30 Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455-5459.

31 (a) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5452-5455. (b) Partyka, D. V.; Robilotto, T. J.; Zeller, M.; Hunter, A. D.; Gray, T. G. *Organometallics* **2007**, *27*, 28-32.

32 Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133-4136.

Phosphine Gold(I) Complexes





A: R^1 = Cy, R^2 = R^3 = H, L = Cl

B: R^1 = *t*-Bu, R^2 = R^3 = H, L = Cl

C: R^1 = *t*-Bu, R^2 = R^3 = *i*-Pr, L = Cl

D: R^1 = Cy, R^2 = OMe, R^3 = H, L = Cl

E: R^1 = *t*-Bu, R^2 = H, L = NTf_2

F: R^1 = Cy, R^2 = *i*-Pr, L = NTf_2

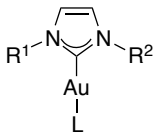
G: R^1 = Cy, R^2 = R^3 = H

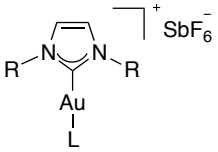
H: R^1 = *t*-Bu, R^2 = R^3 = H

I: R^1 = *t*-Bu, R^2 = R^3 = *i*-Pr

J: R^1 = Cy, R^2 = OMe, R^3 = H

NHC-Gold(I) Complexes





K: R^1 = R^2 = 2,4,6-$Me_3C_6H_2$, L = Cl

L: R^1 = 2,4,6-$Me_3C_6H_2$, R^2 = Me, L = Cl

M: R^1 = R^2 = Me, L = Cl

N: R^1 = R^2 = 2,6-*i*-$Pr_2C_6H_3$, L = Cl

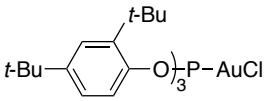
O: R^1 = R^2 = 2,4,6-$Me_3C_6H_2$, L = NTf_2

P: R^1 = R^2 = 2,6-*i*-$Pr_2C_6H_3$, L = NTf_2

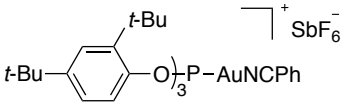
Q: R = 2,4,6-$Me_3C_6H_2$, L = 2,4,6-$(MeO)_3C_6H_2CN$

R: R = 2,6-*i*-$Pr_2C_6H_3$, L = PhCN

Phosphite Gold(I) Complexes

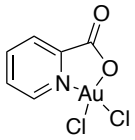


S



T

Gold(III) Complex



U

Figure 3. Gold complexes.

Less electrophilic Au(I) complexes such as **K-N**,[33,28b] cationic **Q** and **R**,[34] as well as neutral **M** and **O**[35,36] and related carbenes,[37] have been synthetized in the presence N-heterocyclic ligands (NHC)[38,39,40] resulting in a family of selective gold(I) catalysts. The most electrophilic catalyst for the activation of alkynes is gold(I) complex **T** bearing a weak donating phosphite ligand.[33a, 41, 42] Neutral complex **S** requires activation by salt metathesis with silver salts such as $AgSbF_6$.[43]

Gold(III) salts and complexes are also used in different catalytic organic transformations. Gold(III) complexes present square-planar

33 (a) Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721-7730. (b) de Frémont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 2411-2418. (c) de Frémont, P.; Singh, R.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2007**, *26*, 1376-1385.

34 (a) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269-279. (b) de Fremont, P.; Stevens, E. D.; Fructos, M. R.; Mar Diaz-Requejo, M.; Perez, P. J.; Nolan, S. P. *Chem. Comm.* **2006**, 2045-2047. (c) de Frémont, P.; Marion, N.; Nolan, S. P. *J. Organomet. Chem.* **2009**, *694*, 551-560.

35 Li, G.; Zhang, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5156-5159.

36 Ricard, L.; Gagosz, F. *Organometallics* **2007**, *26*, 4704-4707.

37 Hashmi, A. S. K.; Lothschütz, C.; Graf, K.; Häffner, T.; Schuster, A.; Rominger, F. *Adv. Synth. Catal.* **2011**, *353*, 1407-1412.

38 Nolan, S. P. *Acc. Chem. Res.* **2010**, *44*, 91-100.

39 Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612-3676.

40 Alcarazo, M.; Stork, T.; Anoop, A.; Thiel, W.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2542-2546.

41 (a) Teller, H.; Flügge, S.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 1949-1953. (b) Teller, H.; Flügge, S.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 1949-1953.

42 Fortman, G. C.; Nolan, S. P. *Organometallics* **2010**, *29*, 4579-4583.

43 López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem.* **2006**, *118*, 6175-6178.

geometry, exhibit higher affinity for hard donor ligands, and are more oxophilic due to their higher oxidation state. Anionic, chelating ligands are commonly employed, such as the picolinate ligand in complex **U**.[44]

Enyne Cycloisomerization

Metal-catalyzed reactions of enynes have been extensively studied for the straightforward synthesis of carbo- and heterocyclic compounds under operationally simple conditions.[6,7,19a,45,46]

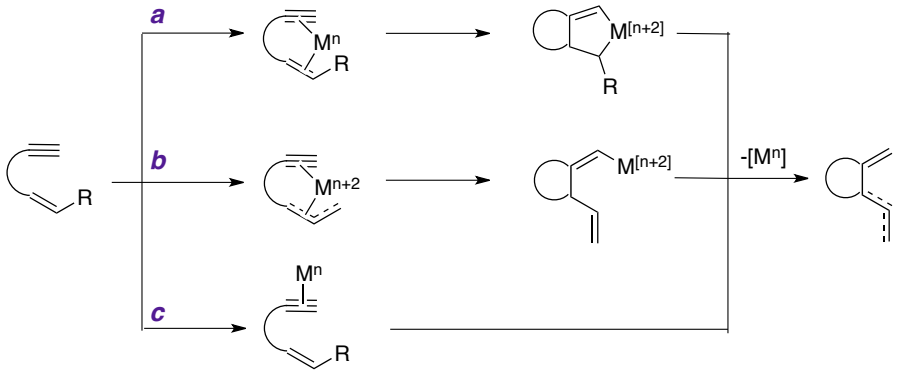
Depending on the reaction conditions and the ligands of the precatalyst, π-complexation with the metal activates the alkyne and/or the alkene of the substrate. Therefore, three main pathways[19a] are possible:

a) Simultaneous coordination of the metal to the alkyne and the alkene forming a metallacyclic intermediate via two-electron oxidation of the metal (pathway **a**, *Scheme 3*).
b) Formation of a π-allyl complex that could further react with the triple bond (pathway **b**, *Scheme 3*). This pathway takes place when a functional group in the allylic position is present in the enyne.
c) Selective activation of the alkyne by the metal centre (pathway **c**, *Scheme 3*).

44 Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejović, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545-6547.

45 Echavarren, A. M; Jiménez-Núñez, E. *Top. Catal.* **2010**, *53*, 924-930.

46 Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215-236.



Scheme 3. Proposed mechanism for the metal-catalyzed cycloisomerization of enynes.

Pathways *a* and *b* operate under the influence of complexes of palladium (0),[47] ruthenium (II),[47] or platinum (II).[48] However, reactions catalyzed by gold can only take place through mechanism c due to: (1) the fact that gold(I) does not undergo oxidative cyclometalations under mild conditions to form gold(III) intermediates;[18d,49] (2) gold complexes have only one labile ligand that can be displaced to allow coordination to the substrate, making the simultaneous coordination to the alkyne and alkene unlikely.

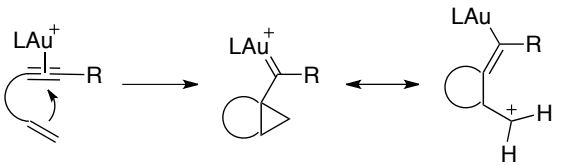
47 Trost, B. M.; Gutierrez, A. C.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 9206-9218.

48 (a) Méndez, M.; Muñoz, M. P.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11549-11550. (b) Baumgarten, S.; Lesage, D.; Gandon, V.; Goddard, J.-P.; Malacria, M.; Tabet, J.-C.; Gimbert, Y.; Fensterbank, L. *ChemCatChem* **2009**, *1*, 138-143.

49 Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511-10520.

1) Gold-Catalyzed Cycloisomerizations of 1,6-Enynes

The gold(I)-catalyzed cyloisomerizations of 1,6-enynes is one of the most studied reactions in gold catalysis. Cationic gold(I) complexes are very active catalysts for the cyclization of 1,6-enynes, and in some cases they facilitate the cycloisomerization of subtrates that are usually unreactive in the presence of other catalysts.[7,45,46, 50]Gold(I) can coordinate to the alkene or alkyne moieties. Selectively activates the alkyne promoting nucleophilic attack by the alkene via π-complexes to form gold intermediates with partial carbene character, and partial carbocationic character.



Scheme 4. Gold(I)-catalyzed activation of alkynes via π-complexes.

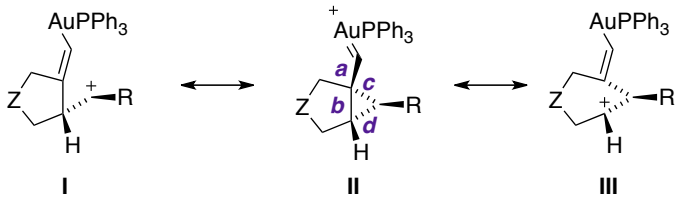
Cyclopropyl gold carbenes are distorted structures, with a short C-C bond connecting the carbene and the cyclopropane C atoms, which can also be represented as gold-stabilized homoallylic carbocations. The cationic or carbenic character of this intermediate is dependent on the ligand present in gold complexes and on the substitution pattern of the enyne (***Table 1***).[28b,51, 56] Therefore, the most relevant resonance structure for enynes where R = H or Me is **III** with a relative long *b* bond. However, when R = *c*-C_3H_5, the

50 Escribano-Cuesta, A.; Perez-Galan, P.; Herrero-Gomez, E.; Sekine, M.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Org. Biomol. Chem.* **2012**, *10*, 6105-6111.

51 (a) Seidel, G.; Mynott, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 2510-2513. (b) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. *Nature Chem.* **2009**, *1*, 482-486. (c) Casanova, J.; Kent, D. R.; Goddard, W. A.; Roberts, J. D. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 15–19.

electron releasing substituent stabilizes positive charge on the adjacent carbon, causing the intermediate to more closely resemble structure **I** in which *c* is the longest bond.

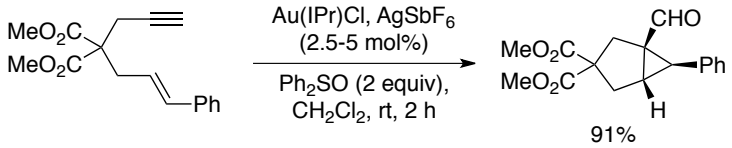
Table 1. Calculated bond distances for intermediate **II**.



R	***a***	***b***	***c***
H	1.378	1.742	1.569
Me	1.372	1.720	1.622
c-C_3H_5	1.356	1.586	1.987

Bond distances in Å determined by DFT (Density Functional Theory) calculations at the B3LYP/6-31G (d) (C,H,P), LANL2DZ (Au) level.

Similar carbene intermediates were first proposed for the electrophilic activation of enynes by Pd(II).[52] More recently, a gold cyclopropyl carbene was intercepted by oxidation with Ph_2SO forming the corresponding aldehyde.[53]

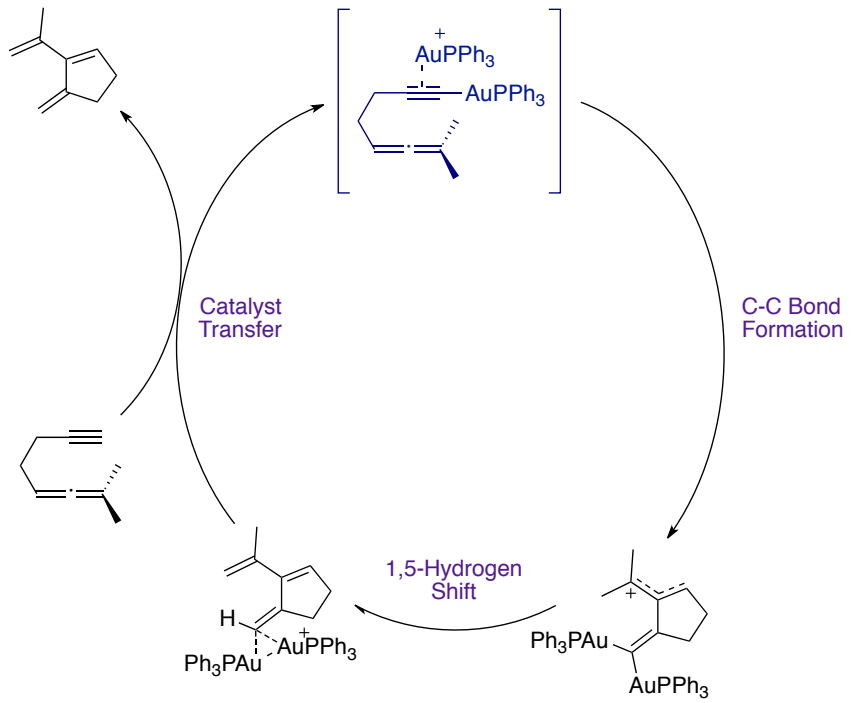


Scheme 5. Trapping of a cyclopropyl gold(I) carbene intermediate.

52 (a) Trost, B. M.; Hashmi, A. S. K. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1085-1087. (b) Trost, B. M.; Hashmi, A. S. K. *J. Am. Chem. Soc.* **1994**, *116*, 2183-2184.

53 Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838-5839.

A dual σ,π-activation[20-24] is also possible.[54] Experimental and computational studies on the cycloisomerization of 1,5-allenynes have shown that these reactions proceed through a unique nucleophilic addition of an allene double bond to a cationic phophinegold(I)-complexed gold(I) acetylide, followed by a 1,5-hydrogen shift (*Scheme 6*).

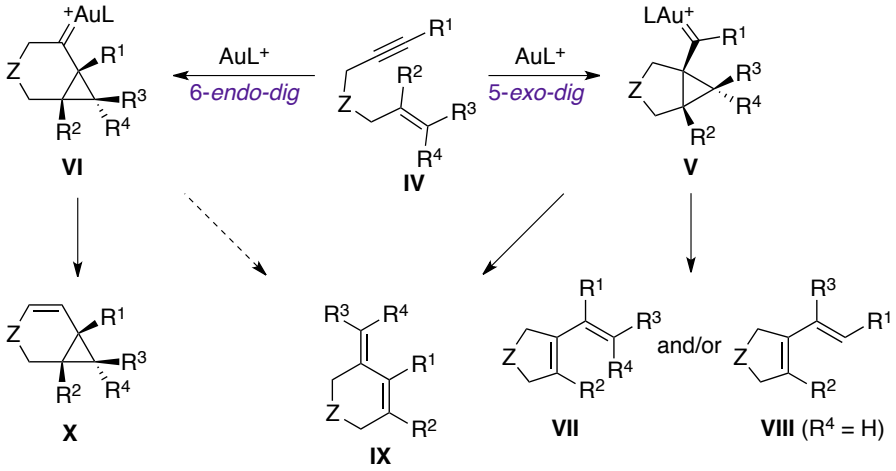


Scheme 6. Mechanism involving a cationic phophinegold(I)-complexed phosphinegold(I) acetylide.

This mechanism is supported by three experimental observations: (1) the inertness of nonterminal alkyne substrates under reaction conditions; (2) deuterium exchange at the terminal alkyne position; (3) observation of the transitory formation of phosphinegold acetylide under the reaction conditions.

54 Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 4517-4526.

In the presence of gold complexes, 1,6-enynes react via *5-exo-dig* or *6-endo-dig* pathways to give cyclization products by different types of skeletal rearrangement.[45a] The major pathways leads to 1,3-dienes **VII**, **VIII** and/or **IX** by single cleavage and double cleavage rearrangements or endocyclic rearrangement, respectively,[49,48a] (*Scheme 7*) and proceed under milder conditions than using alternative metal catalysts.[28b] In these pathways, cyclopropyl gold(I) carbenes (**V** and **VI**) are generated as intermediates. Cyclopropanation products **X** are obtained via 6-*endo*-cyclization followed by proton loss and protodemetalation of intermediate **VI**. [55]

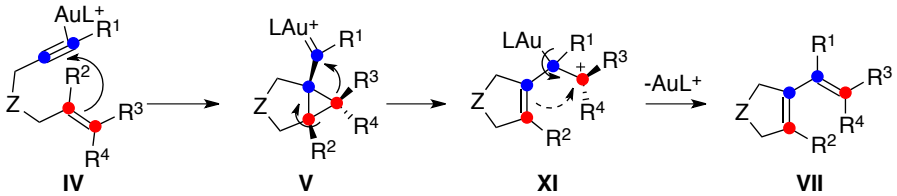


Scheme 7. Major pathways for the Au-catalyzed cyclization of 1,6-enynes.

When the reaction proceeds via 5-*exo-dig* cyclization, dienes **VII** are the products of single cleavage skeletal rearrangement, in which the terminal alkene carbon migrates to the terminus of the alkyne. This transformation may also occur by ring opening of a cyclobutene intermediate. DFT calculations supports that the main pathway for the formation of single-cleavage skeletal rearrangement products proceeds by

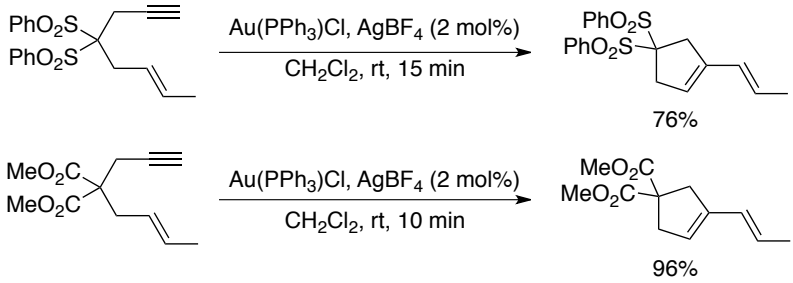
55 Chao, C.-M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Comm.* **2009**, 6988-6990.

opening of intermediate **V** to form the stabilized carbocation **XI**, followed by metal-elimination (*Scheme 8*).[56]



Scheme 8. Single cleavage rearrangement.

Single-cleavage rearrangement catalyzed by gold takes place under mild conditions and in a stereospecific way, in which the configuration of the starting alkene is retained in the final product. Examples of this mode of rearrangement are shown in *Scheme 9*, where simple 1,6-enynes react smoothly at temperatures around -40 to 60 ºC using cationic catalysts **E** or **F**.[60]

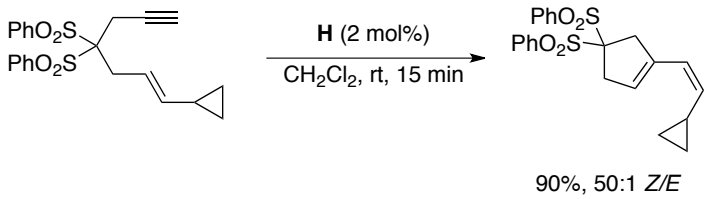


Scheme 9. Formation of 1,3-dienes via single cleavage rearrangement.

As an exception, dienes with a cis configuration, can be formed from 1,6-enyne bearing a strongly electron-donating group attached to the

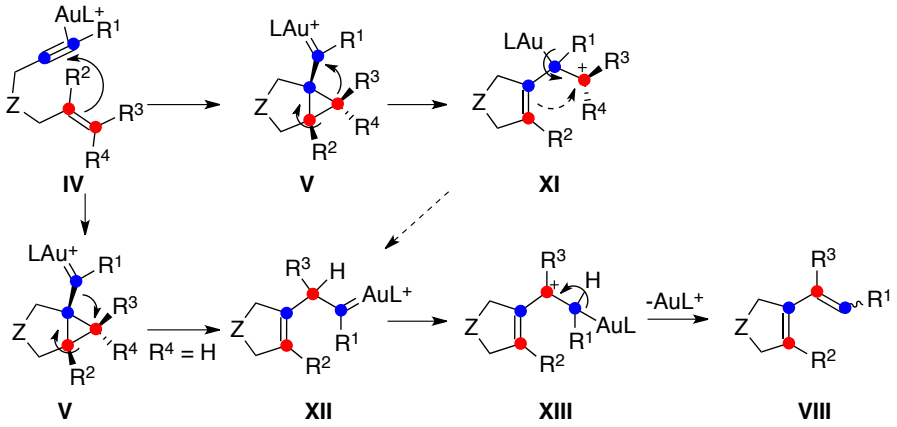
56 Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148.

alkene moiety, regardless of the configuration of the starting enyne (*Scheme 10*).[57]



Scheme 10. Formation of dienes with a *cis* configuration.

Products of type **VIII** result from double cleavage rearrangements in which both the alkene and the alkyne are cleaved. Thus, the *anti*-cyclopropyl gold(I) carbene **V** can either evolve to furnish **VIII** by a formal diatropic rearrangement from **XII**,[58] or by a carbocationic 1,2-shift of the cyclic alkenyl group in **XI**.[28a]

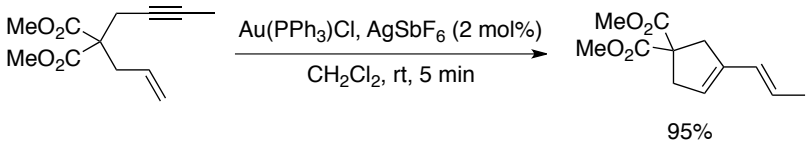


Scheme 11. Double cleavage rearrangement.

57 Jiménez-Núñez, E.; Claverie, C. K.; Bour, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7892-7895.

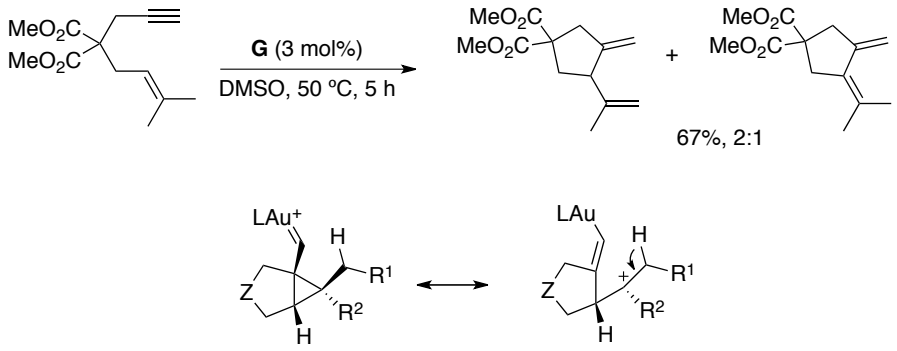
58 (a) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 129-130. (b) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 130-131.

The formation of these kind of products if favored when the starting 1,6-enyne bears an alkyl substituent at the alkyne terminus as is shown in *Scheme 12*, leading product of type **VIII** in excellent yield.[56, 59] Moreover, dienes with predominant or exclusive *Z* configuration have been isolated as products of this type of rearrangement.[52]



Scheme 12. Double cleavage skeleton rearrangement.

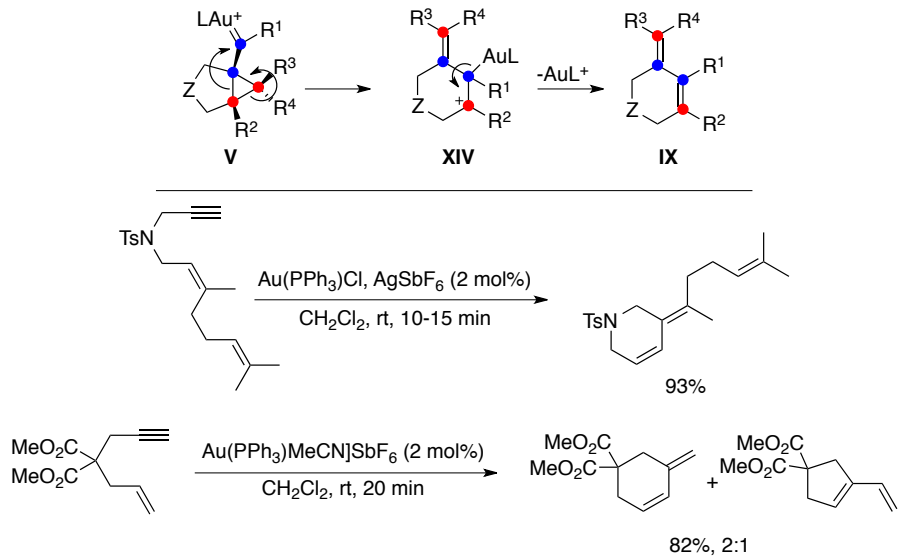
A different mechanistic pathway is followed when the cycloisomerization reaction takes place in DMSO. In this case, a mixture of dienes was formed from an apparent Alder-ene cycloisomerization by proton elimination from the cationic intermediate.[28b]



Scheme 13. Apparent Alder-ene cycloisomerization.

59 Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677-1693.

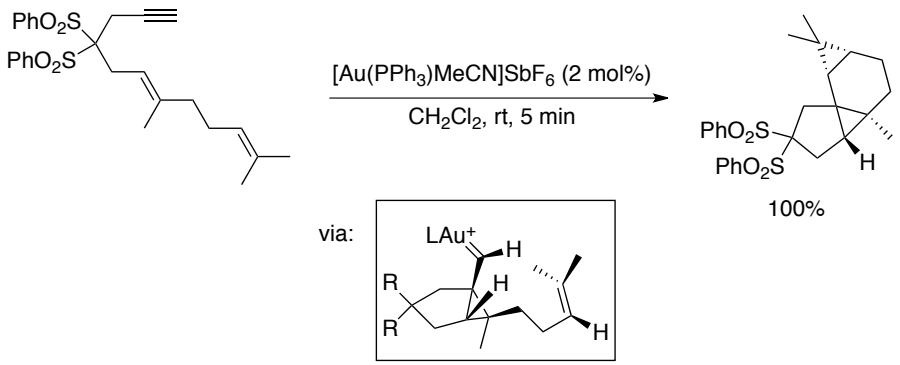
Six-member ring dienes of type **IX** are also formed via 5-*exo-dig* pathway. DFT calculations support their formation from a rearrangement of intermediate **V** to cationic intermediate **XIV**, followed by protodemetalation (*Scheme 14*).[60] These types of products are observed when using 1,6-enynes with terminal unsubstituted alkynes, alkynes or with heteroatoms.[59] As is shown below, when the alkyne and alkene of the enyne are both unsubstituted, mixtures of *endo*- and *exo*-skeletal rearrangement are observed in 2:1 mixture.



Scheme 14. Formation **IX**: Endocyclic skeletal rearrangement.

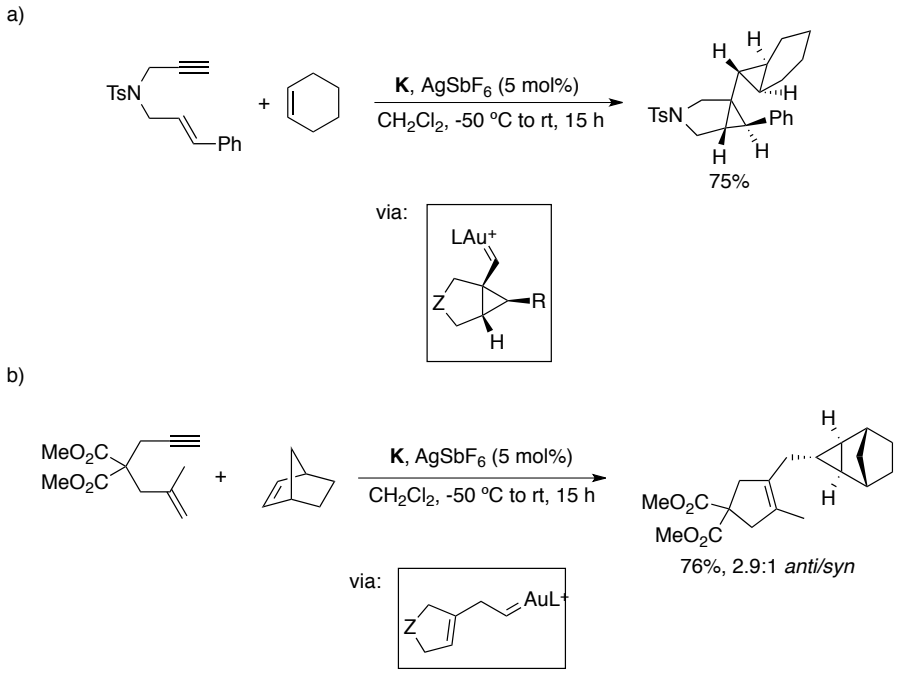
60 Cabello, N.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Eur. J. Org. Chem.* **2007**, *2007*, 4217-4223.

One of the most interesting extensions of gold(I) cycloisomerization of 1,6-enyenes is the intramolecular cyclopropanation of a pendant olefin via an *anti*-cyclopropyl gold(I) carbenes intermediate (*Scheme 15*).[28b] As a result, cyclopropanation products are obtained in a stereoselective way and under mild conditions.



Scheme 15. Intramolecular gold(I)-catalyzed cyclopropanation of 1,6-dienes.

Additionally, this reaction can be carried out intermolecularly by employing either cyclic and acyclic alkenes to capture the *anti*-cyclopropyl gold(I) carbenes leading to the corresponding adducts regio- and stereoselectively (*Scheme 16a*).[43] On the other hand, enynes with a terminal alkene react via a different pathway that involves a rearranged carbene (*Scheme 16b*). In this case a mixture of anti/syn products is observed.

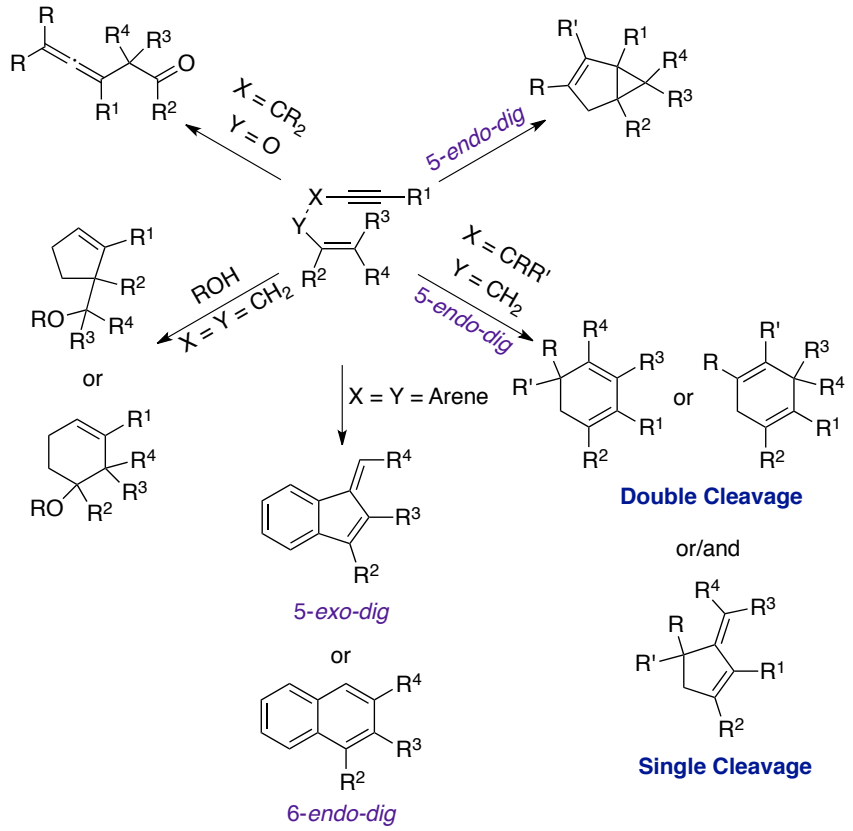


Scheme 16. Interception of cyclopropyl gold(I) carbenes.

2) Gold-Catalyzed Cycloisomerizations of 1,5-Enynes

Reactions of 1,6-enynes have attracted much attention because of the great variety of products that can be obtained from readily available substrates under simple and mild conditions.[45a] The corresponding metal-catalyzed cycloisomerizations of 1,5-enynes have been developed to a much lesser extent. Gold(I) catalyzed cycloisomerization of 1,5-enynes can lead to a range of synthetically useful products by selective coordination of the metal center to the alkyne moiety (*Scheme 17*). [61]

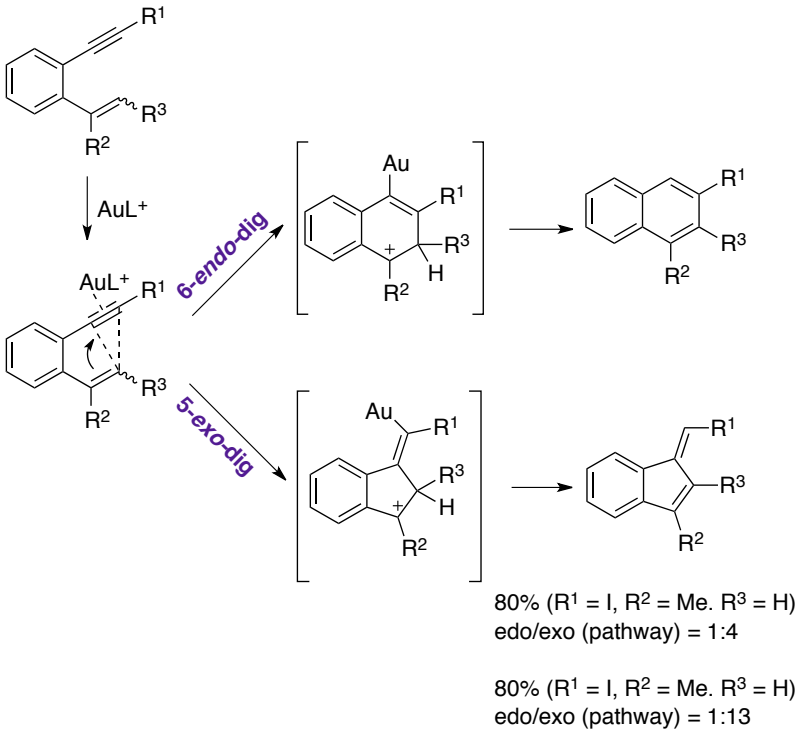
61 Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351-3378.



Scheme 17. General overview for the cyclization of 1,5-enynes.

Generally, 1,5-enynes cyclize through an *endo*-cyclization pathway giving rise to 5 or 6 membered ring products. However, the *exo*-pathway is more favorable when terminal alkynes or iodoalkynes are used leading to naphthalenes and 1-methylene-1*H*-indene derivatives (*Scheme 18*)[62]

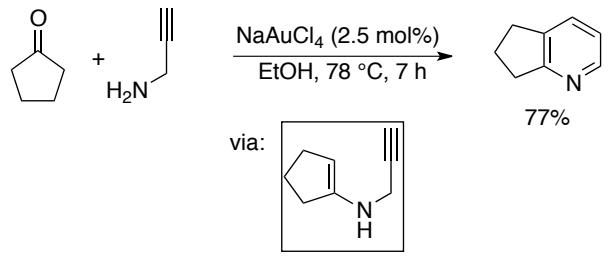
62 Shibata, T.; Ueno, Y.; Kanda, K. *Synlett* **2006**, *3*, 411-414.



Scheme 18. Au(I)-catalyzed cycloisomerization via *endo* or *exo* pathways.

One of the first examples of *endo*-cyclization catalyzed by gold was reported in the context of a new synthesis of pyridines (*Scheme 19*).[63] This transformation proceeds via gold catalyzed condensation between the ketone and the propargylamine to give an imino intermediate followed by imine-enamine isomerization. A regioselective 6-*endo-dig* cyclization followed by a dehydrogenation of the resulting dihydropyridine affords the formation of pyridine derivates.

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



Scheme 19. Synthesis of pyridines by cyclization f 1,5-enynes.

As reported for 1,6-enynes, 1,5-enynes can undergo single and double cleavage skeletal rearrangements. A mechanistic discussion of gold(I) catalyzed cyclization of 1,5-enynes will be presented extensively in Chapter 1.

3) Gold-Catalyzed Cycloisomerizations of 1,n-Enynes (n>6)

Cyclization of 1,7-enynes has normally been examined as an extension of the cyclization of 1,6-enynes.[64] In general, gold(I) complexes undergo the cyclization with lower catalyst loading and under milder conditions than with other metal catalyst.[65, 66,67, 68]

Thus, a variety of 1,7-enynes bearing different substituents at the alkene moiety react with cationic gold(I)-complexes to give dienes as the final product of single cleavage (*Scheme 20a*). Furthermore, 7-*exo-dig*

64 (a) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049-6050. (b) Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104-9105.

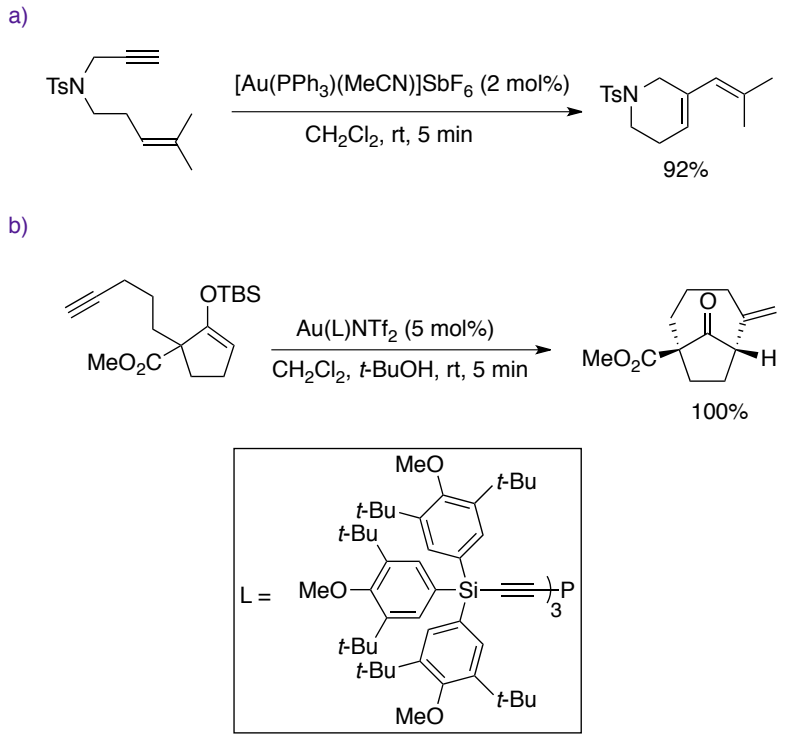
65 Simmons, E. M.; Sarpong, R. *Org. Lett.* **2006**, *8*, 2883-2886.

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

67 Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 714-715.

68 Cabello, N.; Rodíguez, C.; Echavarren, A. M. *Synlett* **2007**, *2007*, 1753-1758.

cyclization has been observed for 1,7-enynes bearing a silyl enol ether moiety (*Scheme 20b*) in the presence of gold(I)-complexes containing a semihollow-shaped triethynylphosphine.[69] Cyclization of related 1,8-enynes also gives seven-membered ring compounds.[69]



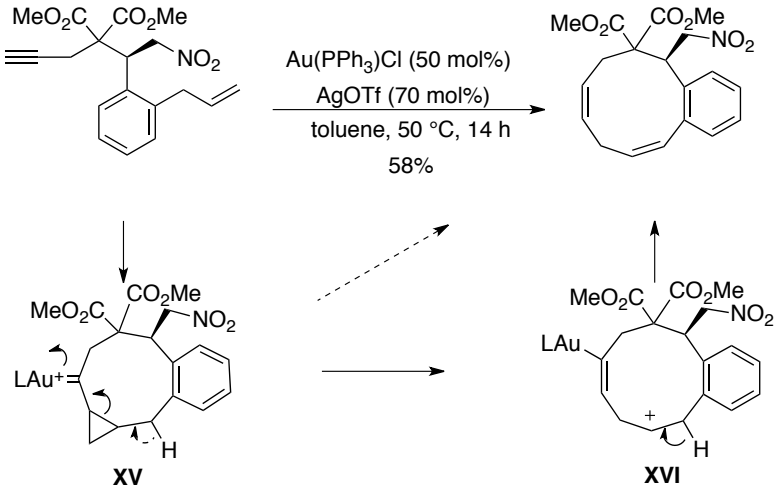
Scheme 20. Au(I)-catalyzed skeletal rearrangement of 1,7-enynes.

The largest 1,n-enyne that has been reported to participate in cycloisomerization reactions in the presence of gold catalyst is a 1,9-enyne (*Scheme 21*).[70] The formation of 10-membered ring from 1,9-enynes requires high catalyst loading. This cyclization is reported to occur via intermediates

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

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

XV and **XVI**, although intermediate **XV** could also evolve to give the product directly.

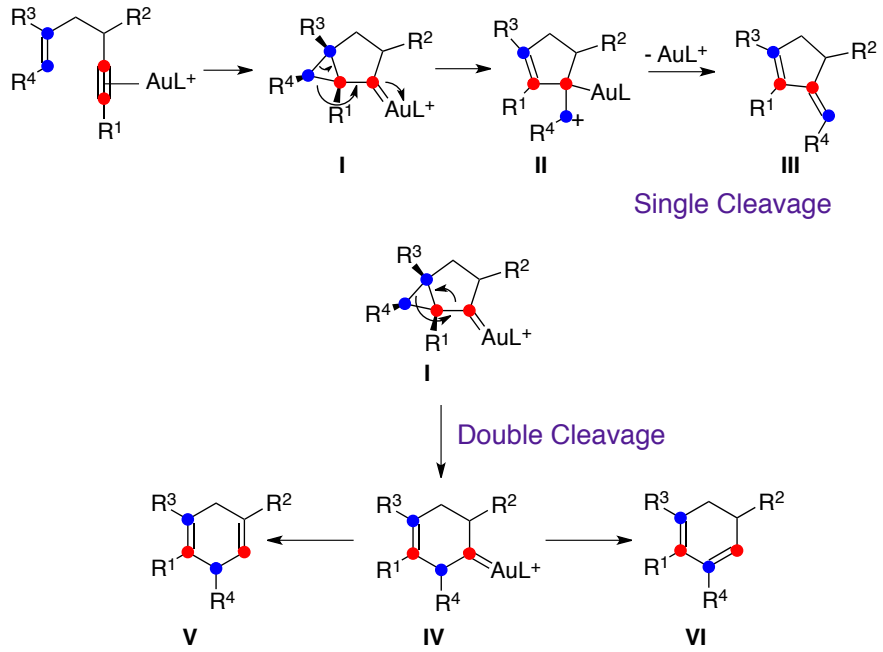


Scheme 21. Gold(I)-catalyzed cyclization of 1,9-enynes.

Chapter 1. Cycloisomerization of 1,5-Enynes

1.1 Introduction

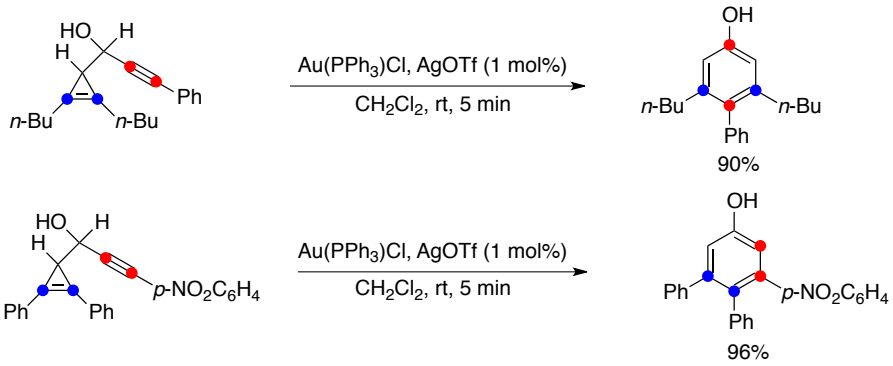
As reported for 1,6-enynes, the gold-catalyzed cyclization of 1,5-enyes can also proceed via single cleavage rearrangement[1] via the formation of cyclopropyl gold carbenes **I** (*Scheme 1*).[3a] Opening of **I** to carbocation **II**, followed by demetalation would give **III**. An alternative evolution of intermediates **I** has been shown to give six-membered rings[3b] in a mechanistically intriguing transformation that involves a double cleavage rearrangement of 1,5-enynes. Thus, a rearrangement could give **IV** by a process reminiscent of that found in the double cleavage rearrangement of 1,6-enynes. Deprotonation and demetalation then affords 1,4-cyclohexadienes **V** or **VI**.



Scheme 1. Single and double cleavage rearrangement *via* a cyclopropyl gold carbene.

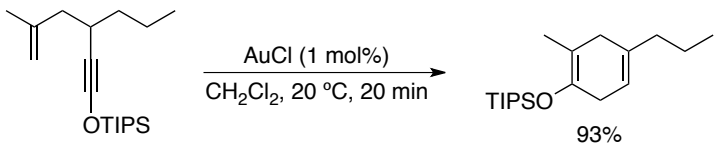
1 Gagosz, F. *Org. Lett.* **2005**, *7*, 4129-4132.

A notable example of double cleavage rearrangement occurs during the cyclization of 1,5-enynes containing alkyl substituted cyclopropenes, giving rise to phenols in high yields and under mild condition (*Scheme 2*).[2] However, 1,5-enynes bearing aromatic substituents at the cyclopropene undergo rearrangement without cleavage of either the alkyne or alkene as shown below for a 1,5-enynes bearing two phenyl substituents.



Scheme 2. Double cleavage cyclization of 1,5-enynes.

Double cleavage rearrangement has also been observed in the cycloisomerization of silyloxy-1,5-enynes when AuCl is used as catalyst.[3] In this case, 1,4-cyclohexadienes are obtained in excellent yield and with low catalyst loading as is shown in *Scheme 3*.

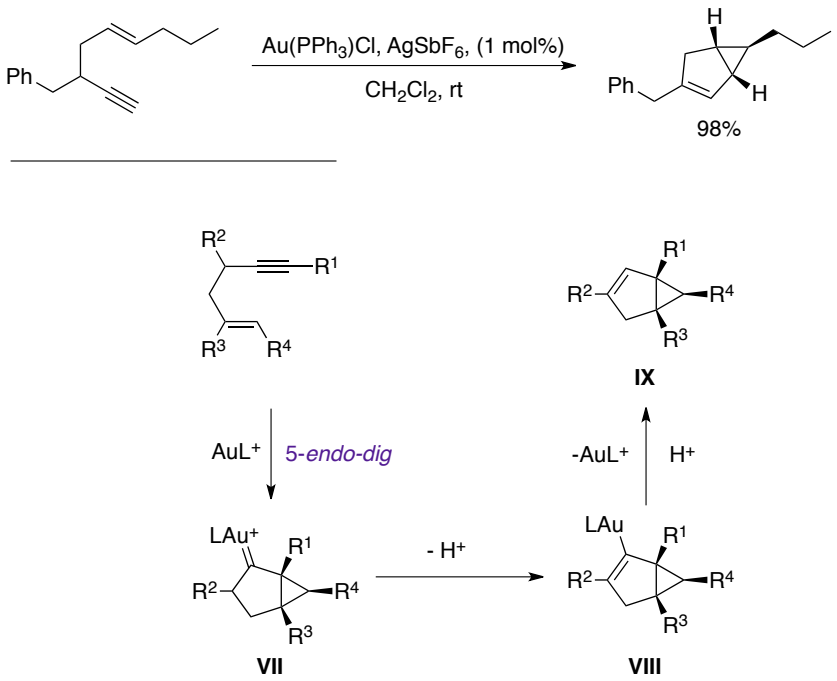


Scheme 3. Double cleavage rearrangement: Formation of 1,4-cyclohexadienes.

2 Li, C.; Zeng, Y.; Zhang, H.; Feng, J.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 6413-6417.

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

Bicyclo[3.1.0]hexenes are also common products of the gold-catalyzed cycloisomerization of 1,5-enynes. These bicycles were obtained before as the major constituent of a complex mixture produced by the thermal rearrangement of 1,5-enynes.[4] The use of gold catalysis allows these products to be formed in a stereospecific way and in high yields via *5-endo-dig* cyclization with formation of cyclopropyl gold(I) carbene **VII** (*Scheme 4*).[5] This intermediate evolves by deprotonation to form alkenyl gold complexes **VIII** followed by protonolysis to give the desired bicyclo[3.1.0]hexenes **IX**. [5,6]



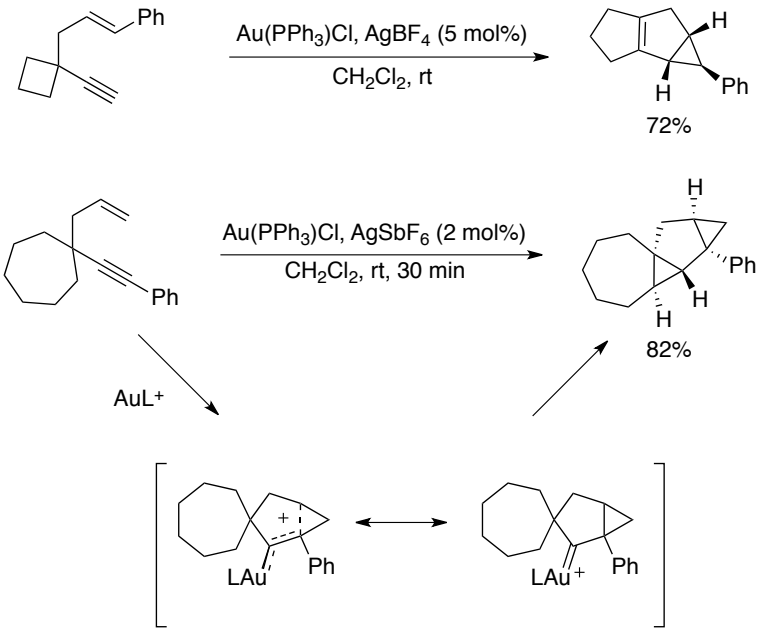
Scheme 4. Mechanism: Gold(I)-catalyzed cyclization of 1,5-enynes.

4 Mazur, M. R.; Potter, S. E.; Pinhas, A. R.; Berson, J. A. *J. Am. Chem. Soc*. **1982**, *104*, 6823-6824.

5 (a) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654-8655. (b) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858-10859.

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

1,5-Enynes bearing cycloalkanes at the propargylic position also cyclize in the presence of gold(I) complexes leading to tricyclic products as a result of a 1,2-alkyl shift. However, substrates with larger rings evolve through a C-H activation mechanism, delivering fused tetracyclic products (*Scheme 5*).[7]



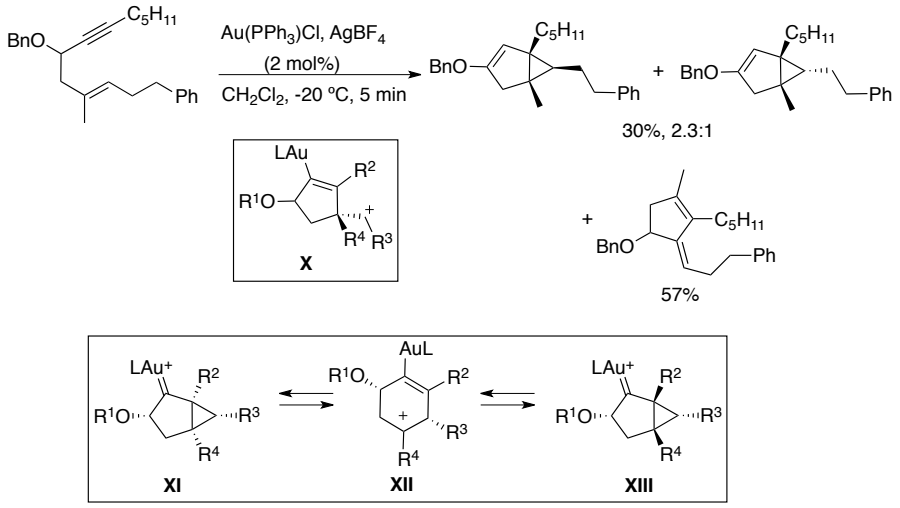
Scheme 5. Examples of gold(I)-catalyzed cycloisomerizations of 1,5-enynes.

Mixtures of products are often formed in the cycloisomerization of 1,5-enynes due to competitive operation of more than one rearrangement pathway. DFT studies have demonstrated that there are several energetically accessible pathways, and that course taken during the reaction is sensitive to the nature of gold catalyst used and the substituents on the enyne.[8] As an example, three different products are obtained in the cyclization of

7 (a) Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2809-2811. (b) Liu, Y.; Zhang, D.; Zhou, J.; Liu, C. *J. Phys. Chem. A.* **2010**, *114*, 6164-6170.

8 Fan, T.; Chen, X.; Sun, J.; Lin, Z. *Organometallics* **2012**, *31*, 4221-4227.

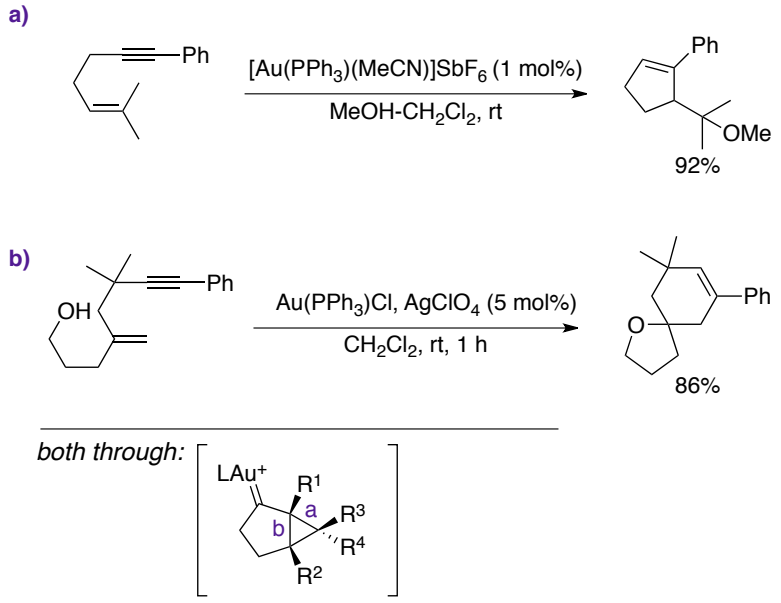
benzyloxy enynes in the presence of gold complexes (*Scheme 6*): the expected bicyclo[3.1.0]hexene product together with its stereoisomer, alongside the major product resulting from single cleavage rearrangement. The stereospecificity of this reaction can be explained by the opening of cyclopropyl gold(I) carbene **XI** to a six-membered ring carbocation **XII** or the cyclopentenyl cation **X**. Intermediate **XII** has been intercepted by an *O*-Boc group in reactions of Boc-protected hex-1-en-5-yn-3-ols, affording cyclohex-4-ene-1,2-diol derivatives.[9]



Scheme 6. Cyclization of benzyloxy enyne and its possibles intermediates.

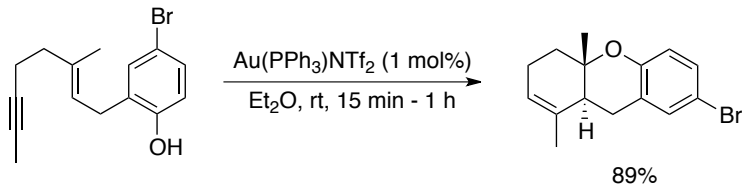
1,5-Enynes also react with nucleophiles such as water or alcohols in the presence gold(I) complexes to give the corresponding products of hydroxy- or alkoxycyclization (*Scheme 7*).[6] Cleavage of bond ***a*** in the cyclopropyl gold(I) intermediate gives cyclopentenes as products. However the intramolecular hydroxycyclizations of 1,5-enynes to give six-membered ring derivatives take place by cleavage of bond ***b***.

9 Lim, C.; Kang, J.-E.; Lee, J.-E.; Shin, S. *Org. Lett.* **2007**, *9*, 3539-3542.



Scheme 7. Gold(I)-catalyzed hydroxy- and alkoxycyclizations of 1,5-enynes.

In a similar way to hydroxyl-1,5-enynes, phenols[10] and electron rich arenes[11] also react intramolecularly with 1,5-enynes leading to tricyclic products.



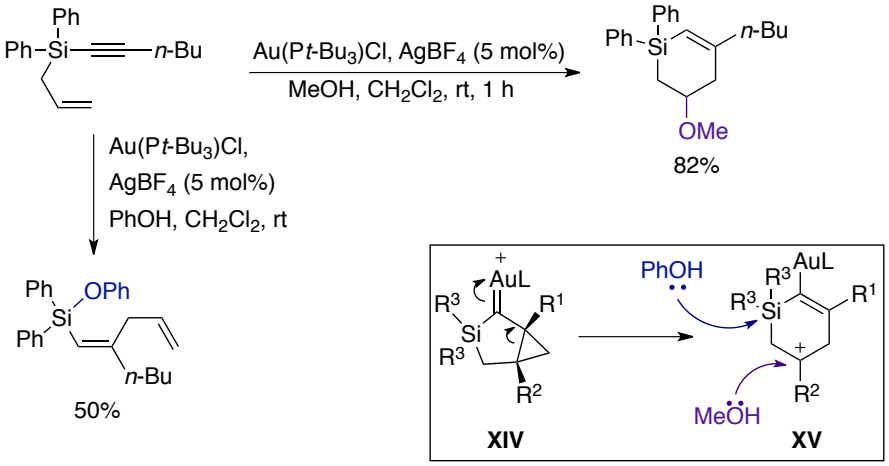
Scheme 8. Gold(I)-catalyzed intramolecular reaction of phenols with 1,5-enynes.

Allyl silyl alkynes also react with gold(I) complexes in the presence of alcohols via endocyclic cleavage of the cyclopropyl gold carbene intermediate. Intermediate **XIV** can evolve via **XV** either by attack of the

10 Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett.* **2009**, *11*, 2888-2891.

11 Pradal, A.; Chen, Q.; Faudot dit Bel, P.; Toullec, P. Y.; Michelet, V. *Synlett* **2012**, 74-79.

nucleophile at the carbocationic center, or at the silicon atom to give the corresponding adducts of alkoxycylization or alkenylsilanes.



Scheme 9. Gold(I)-catalyzed reaction of allyl silyl alkynes with MeOH

1.2. Objectives

Although ligands play a major role in the control of the regio or site selectivity in the gold catalyzed cyclization of 1,6-enynes,[12, 13] the effects on the cyclization of 1,5-enynes has not been examined systematically. Thus, one of the objectives of this work was to develop a new cycloisomerization of 1,5-enynes while studying the effect of the ligands in cyclization of 1,5-enynes. Moreover, we were interested in trapping the intermediate cyclopropyl *endo*-carbenes formed in the reaction to justify the carbene character of them.

To date, some examples of the application of gold catalyzed cyclization of 1,6-enynes to the total synthesis of natural product such as (-)-englerin A[14] or orientalol F[15] have been reported. However, so far there have not been any reported natural product syntheses that make use of a gold-catalyzed 1,5-enyne cyclization.

The second objective of this work was to apply the developed gold(I) catalyzed cyclization methodology for the total synthesis of anhydrocannabimovone, a terpenoid with strong activity at both ionotropic and metabotropic cannabinoid receptors (*Scheme 10*). [16,17]

12 Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351-3378.

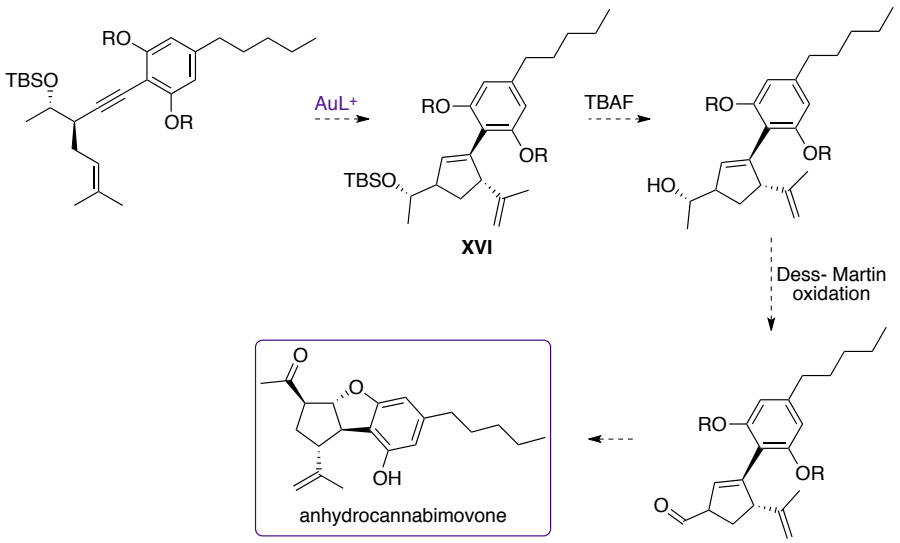
13 Pérez-Galán, P.; Martin, N. J. A.; Campaña, A. G.; Cárdenas, D. J.; Echavarren, A. M. *Chemistry – An Asian Journal* **2011**, *6*, 482-486.

14 (a) Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3517-3519. (b) Zhou, Q.; Chen, X.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 3513-3516.

15 Jiménez-Nuñez, E.; Molawi, K.; Echavarren, A. M. *Chem. Comm.* **2009**, 7327-7329.

16 Turner, C. E.; Elsohly, M. A.; Boeren, E. G. *J. Nat. Prod.* **1980**, *43*, 169-234.

17 Taglialatela-Scafati, O.; Pagani, A.; Scala, F.; De Petrocellis, L.; Di Marzo, V.; Grassi, G.; Appendino, G. *Eur. J. Org. Chem.* **2010**, 2067-2072.



Scheme 10. Application towards the synthesis of anhydrocannabimovone.

The work carried out on this synthesis has led to the preparation of intermediate **XVI**. This work is part of a broader study in collaboration with the graduate student Maria Kirillova and will not be included in this PhD manuscript.

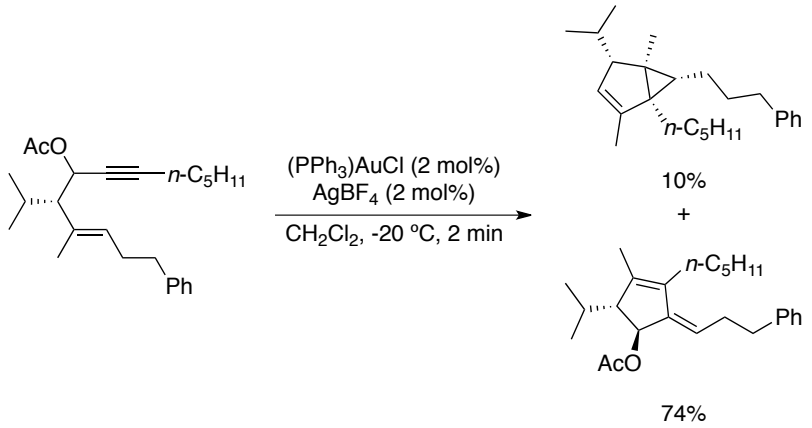
1.3. Results and Discussion[18]

The cycloisomerizarion of 1,5-enynes has attracted interest due to the variety of products[1,19] that can be formed containing five-membered or six-membered rings which could be precursors for many successive synthetic applications. Different mechanistic proposals have been reported for the formation of the cycloisomerization products. Nevertheless, the outcome of such 1,5-enynes cyclizations is often difficult to predict. Different substituents at the enyne or changes on the gold(I)-complexes can lead to different products under reaction conditions which are otherwise unchanged.

Cyclization of 1,5-enynes is known to be a fast processes even at low temperature (*Scheme 11*).[1] By altering the electronics of 1,5-enyne substrates (using electron rich or electron poor substrates) and playing with the nature of the ligands of the gold(I)-complexes we thought that it would be possible to control the cyclization outcome.

18 (a) Work developed in collaboration with V. López-Carrillo, and Á. Mosquera. (b) López-Carrillo, V.; Huguet, N.; Mosquera, Á.; Echavarren, A. M. *Chem. Eur. J.* **2011**, *17*, 10972-10978.

19 Grisé, C. M.; Barriault, L. *Org. Lett.* **2006**, *8*, 5905-5908. (b) Grisé, C. M.; Rodrigue, E. M.; Barriault, L. *Tetrahedron* **2008**, *64*, 797-808. (c) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liébert, C.; Menz, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 2310-2313. (d) Lee, Y.-U.; Lim, C.-M.; Kim, S.-H.; Shin, S.-H. *Bulletin of the Korean Chemical Society* **2010**, *31*, 670-677.



Scheme 11. Cyclization of 1,5-enynes at low temperature.

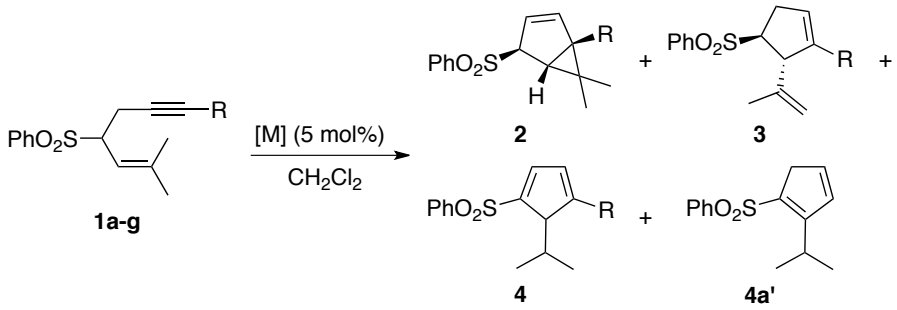
In a first attempt, the nucleophilicity of the alkyne present in the 1,5-enyne was decreased by introducing an electron poor group at the propargylic position. In a previous study that 1,5-enynes bearing acetates, benzyl ethers or methoxy groups at the propargylic position in the presence of gold complexes and under mild conditions gave a complex mixture of products or undergo decomposition by the ready formation of allyl cations.[20] Thus, we decided to replace these groups with a sulfone moiety.

Gold complexes **H**, **R**, **T** and platinum catalyst **W** were chosen as catalysts of different electrophilicity. Reaction of 1,5-enyne **1a** with 5 mol% of catalyst **R** in CH_2Cl_2 at room temperature gave bicyclo[3.1.0]hexene **2a** as the major product (*Table 1*, entry 1), whereas more electrophilic catalyst **H** led to cyclopentadiene **4a'** (*Table 1*, entry 2). Extensive decomposition was observed with catalyst **T**, which led to **4a'** in low yield (*Table 1*, entry 3). Reaction with $AuCl_3$ proceeded at 80 ºC in toluene to give 51% of a 1:1 mixture of **2a** and **3a** (*Table 1*, entry 4). Platinum(II) complex **W** also led to **2a** as the major product (*Table 1*, entry 5), while a complex mixture was observed with $PtCl_4$. The

20 López-Carrillo, V. *Doctoral Thesis* **2010**, ICIQ.

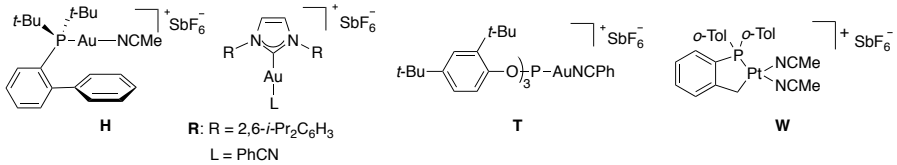
bicyclo[3.1.0]hexene derivatives did not undergo isomerization via vinylcyclopropane rearrangement under the reaction conditions.[21]

Table 1. Cyclization of 1,5enynes **1a-g** with gold(I) and platinum(II) metal catalysts.



entry	R (enyne)	[M]	T (ºC)	t (h)	product (Yield %)
1	H (**1a**)	**R**	23	16	**2a**+**3a**+**4a'** (10:1:4, 74)
2	H (**1a**)	**H**	100[a]	0.3	**4a'** (87)
3	H (**1a**)	**T**	23	1	**4a'** (23)
4	H (**1a**)	$AuCl_3$	80[b]	14	**2a**+**3a** (1:1, 51)
5	H (**1a**)	**W**	23	16	**2a**+**3a**+**4a'** (10:2:1, 69)
6	Me (**1b**)	**T**	23	24	**3b** (80)
7	Et (**1c**)	**T**	23	24	**3c** (52)
8	Ph (**1d**)	**R**	23	18	**2d** (50)
9	Ph (**1d**)	**T**	23	17	**3d** (67) + **4d** (25)
10	*p*-MeC_6H_4 (**1e**)	**T**	23	16	**3e** (58) + **4e** (21)
11	*p*-$MeOC_6H_4$ (**1f**)	**T**	23	16	**3f** (58) + **4f** (28)

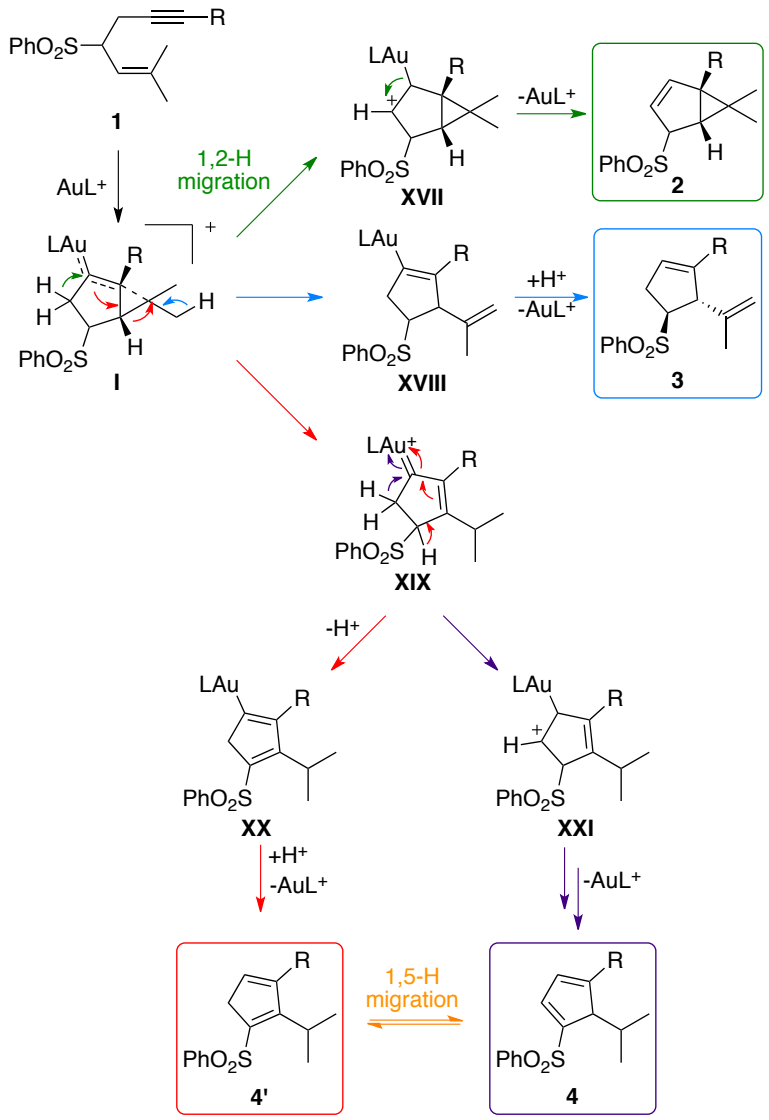
[a] Microwave heating. [b] Reaction in toluene.



21 Reeds, J. P.; Whitwood, A. C.; Healy, M. P.; Fairlamb, I. J. S. *Chem. Comm.* **2010**, *46*, 2046-2048.

Reaction of **1b** and **1c** in the presence of catalyst **T** gave 1,4-dienes **3b** and **3c** exclusively (*Table 1*, entries 6 and 7). As expected, phenyl substituted enyne **1d** gave rise to **2d** with catalyst **R** (*Table 1*, entry 8). Reaction of **1d** with complex **T** led to **3d** along with 25% yield of **4d** (*Table 1*, entry 9). Cyclopentadiene **4d** was obtained as a single isomer that slowly equilibrated to give 3.6:1:1 mixture of three cyclopentadienes by 1,5-H sigmatropic migration. Cyclization of enynes **1e-f** in the presence of catalyst **T** also gave mixtures of 1,4-dienes **3e-f** and cyclopentadienes **4e-f** (Table 1, entries 10 and 11).

Scheme 12 illustrates the mechanistic rationale for the formation of the different products in the cyclization of 1,5-enynes.

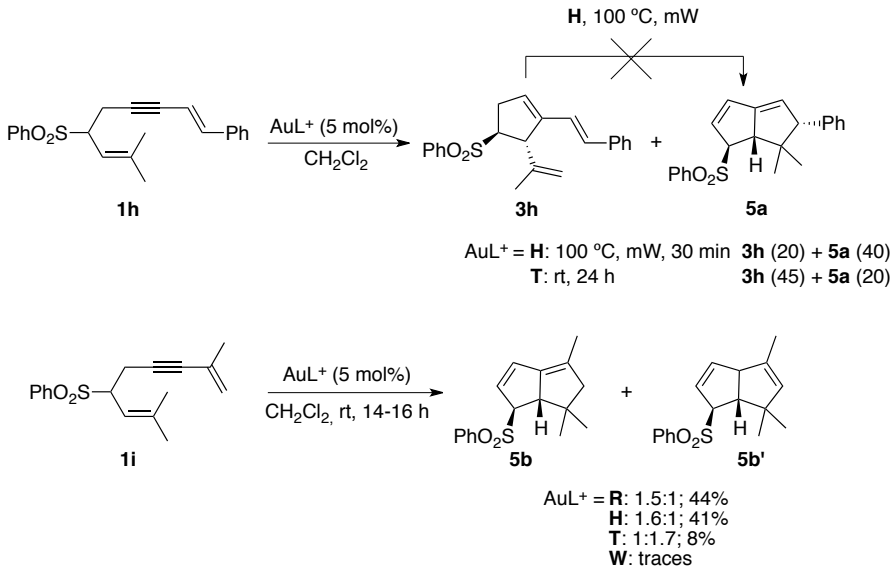


Scheme 12. Proposed mechanism for the formation of different cyclized products.

Bicyclo[3.1.0]hexene **2** is formed via 1,2-hydrogen migration of intermediate **I** followed by demetallation of **XVIII**. A second pathway led to 1,4-dienes via deprotonation of **I** to form neutral vinyl gold intermediate **XIX**, which undergoes protodemetallation to form **3**. A third pathway begins from intermediate **I** with an alternative hydride migration leading to an α,β-unsaturated gold(I) carbene **XX**, which forms intermediate **XXI** by

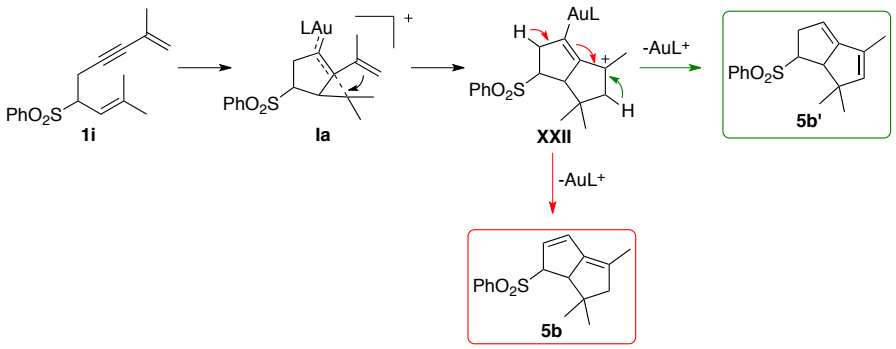
loss of the vinylic proton. Finally, protodemetallation of **XXI** leads to diene **4'**. Additionally, two consecutive 1,5-H migrations from **4'** explains the formation of 1,3-diene **4**. Alternatively, **4** could be formed from **XXI** by demetallation and 1,2-H shift.

Vinyl-substituted enynes **1g-h** were also studied. Cyclization of enyne **1g** with catalyst **H** under microwave irradiation led to the expected product **3g** along with **5a** as the major product (*Scheme 13*). The product ratio was inverted when the reaction was carried out with more electrophilic complex **T** as catalyst at room temperature for 24 h. Tetrahydropentalene **5a** is formed via an intermediate of type **Ia** (*Scheme 13* and *Scheme 14*) and not by gold(I)-catalyzed cyclization of **3g** because heating this triene with catalyst **H** at 100 ºC (microwave irradiation) for 30 min failed to give **5a**.



Scheme 13. Cyclization of 1,5-enynes **1g-h** with gold(I) complexes.

Mechanistically, this annulation is related to that occurring in the gold(I)-catalyzed [4+2] cycloaddition of dienynes[13,22] and in the cyclization of 1,8-dien-4-ynes,[23] in which the pendant alkenes act as the internal nucleophiles (*Scheme 14*). Cyclization of enyne **1h** in the presence of catalyst **R** resulted in the formation of 1.5:1 mixture of bicyclic products **5b**/**5b'** in moderate yield. In contrast, the use of the most electrophilic gold(I)-complex **T** gave inversion of the selectivity and lower yield. When the reaction was carried out with platinum complex **W** only traces of **5b**/**5b'** were observed.



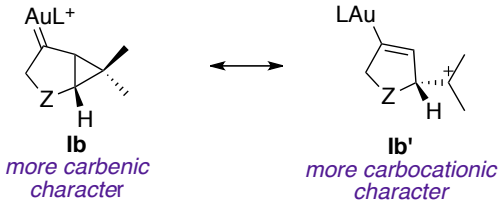
Scheme 14. Proposed mechanism for the formation of **5b** and **5b'**.

From the results reported above on the cycloisomerization of 1,5-enynes we have demonstrated the effect that the nature of the ligand at gold(I)-complex have in the outcome of the reaction. Thus, reaction of gold complexes with highly electron-donating N-heterocyclic carbene ligands (complex **R**) gave cyclopropyl compounds as cyclized product via intermediate **Ib** with a more carbenic character. In this case, the donating

22 (a) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178-6179. (b) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269-279.

23 Böhringer, S.; Gagosz, F. *Adv. Synth. Catal.* **2008**, *350*, 2617-2630.

ligand increases the electron density at the metal center favoring increased back bonding from gold to the cyclopentenyl ring in the intermediate **I** in comparison with complexes bearing less donating ligands such as phosphite derivatives. Therefore, reaction with phosphite-gold complex **T** can be better interpreted as proceeding via more carbocationic intermediates **Ib'** to lead to the formation of 1,4-dienes.



Scheme 15. Character of the intermediate **I**.

This ligand effect has also been corroborated by DFT calculations on a series of 1,5-enyne models (*Figure 1*). For comparison, Pt(II) intermediates **6** and free carbocations **7a** (R=H) and **7b** (R=Me) were also included in this study.

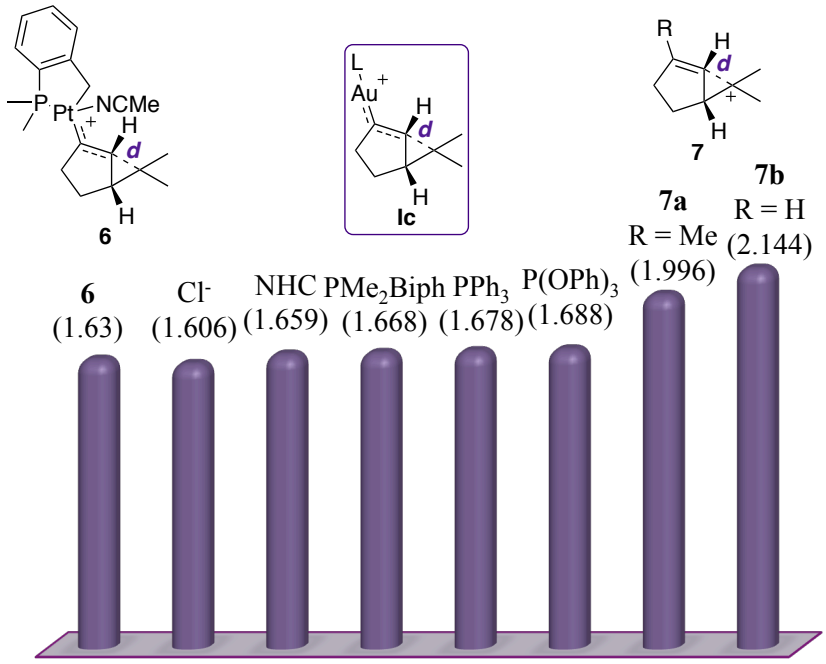
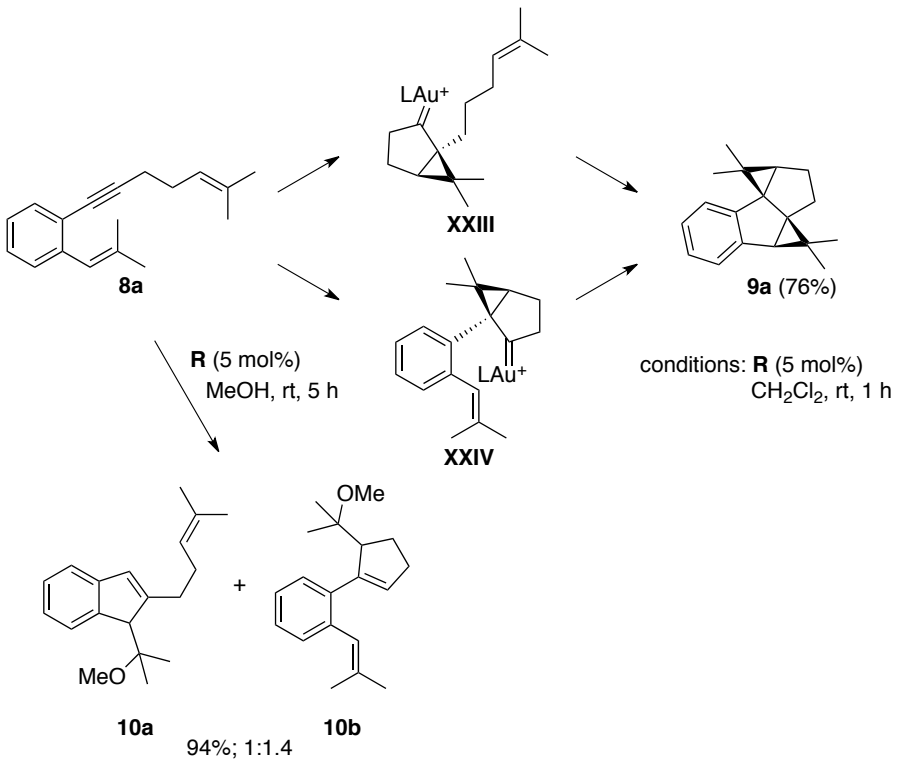


Figure 1. Variation of distance, *d* [Å], in gold intermediates **Ic** as a function of ligand L (NHC = *N,N'*-diphenylimidazolydene, Biph = biphenyl). The bars originate at 1.4 Å to highlight the relative differences (DFT, B3LYP/6-31G**, LANL2DZ (Au)).

Calculations show that metal-stabilized intermediates are significantly different from simple homoallylic carbocations **7a**,**b**. Intermediate **Ice** (L=$P(OPh)_3$) shows the longest bond length (1.688 Å) of the gold(I) complexes, but this distance is still 0.3 Å shorter than a classic carbocation, such as **7b** (R=Me). In contrast, intermediate **Ica** with a strongly electron-donating ligand, such as Cl^-, presents the shortest bond (1.606 Å), which corresponds more closely to a cyclopropyl gold(I) structure. Although the effect is not dramatic, the bond lengths increase along the series Cl^- < *N,N'*-diphenylimidazolydene (NHC) < PMe_2Biph < PPh_3 < $P(OPh)_3$, which correlates with the decreasing donor ability of L.

Additionally, according to these calculations we should be able to trap intermediate **I** with alkenes in the cyclization of 1,5-enynes using gold(I) complexes bearing high donating ligands such as **R**, to enhance the carbene character of the intermediate. Thus, diene **8a**, which has two alkene groups in a 1,5-relationship to the alkyne, reacted in the presence of gold(I)-complex **R** to give pentacylic biscyclopropane derivative **9a** in 76% yield (*Scheme 16*).



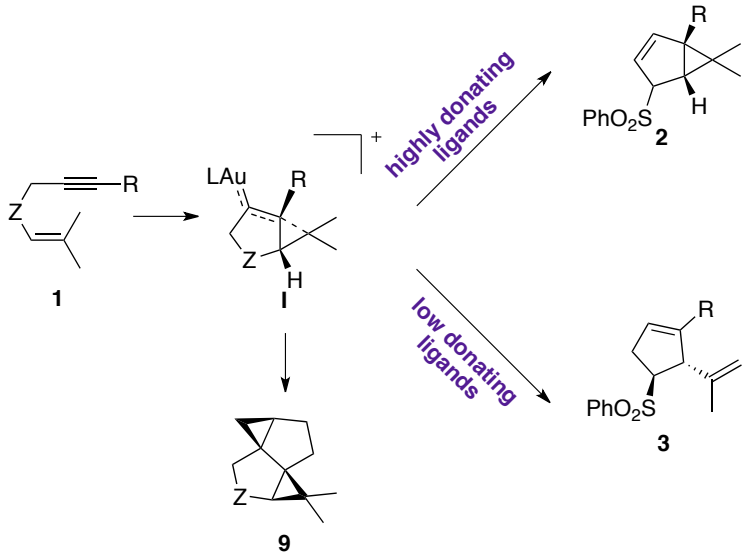
Scheme 16. Gold(I)-catalyzed cyclization of dienyne **8a**.

Interestingly, in this case, the formation of pentacyclic biscyclopropane derivative **9a** could occur by two parallel pathways via intermediates **XXII** and/or **XXIII**, which would converge to form the same pentacyclic product. Both intermediates are likely to be formed in this transformation, since a similar gold(I)-catalyzed reaction carried out in

MeOH let to a 1:1.4 mixture of adducts **10a** and **10b**, product of the attack of MeOH to intermediates **XXII** and **XXIII** respectively. In the presence of the most electrophilic catalyst **T**, the methoxycyclization reaction gave a 1:5 mixture of **10a** and **10b**.

1.4. Conclusions

The carbene or carbocationic nature of the intermediates in the gold-catalyzed cycloisomerization of 1,5-enynes can be tuned depending on the ligands environment of the gold catalyst. Gold(I) complexes with highly electron-containing *N*-heterocyclic ligands enhanced the carbene-like character of the intermediates promoting reactions that proceed via intermediates with carbene-like character, leading to products with a bicyclo[3.1.0]hexene skeleton.



The intermediate cyclopropyl *endo*-gold carbene can be trapped to form biscyclopropane derivatives for the first time, in a reaction that proceeds in a concerted fashion, according to DFT calculation. This work further emphasizes that the intermediates in gold(I)-catalyzed cyclization of 1,5-enynes are significantly stabilized homoallylically and are not open carbocations.

1.5. Experimental Section

General Procedures

All reactions were carried out under Ar in solvents dried using a Solvent Purification System (SPS). Thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck GF_{234}). Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm) or automated flash chromatographer CombiFlash Companion. NMR spectra were recorded at 23 ºC on a Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatus. Mass spectra were recorded on a Waters LCT Premier (ESI) and Waters GCT (EI, CI) spectrometers.

Complex **F** was used as received from Aldrich. The following gold(I) complexes were prepared according to described procedures: **G**,[24] **I**,[24] **Q**,[25] **R**,[25] **T**,[25] **W**[26] and **U**[27].

Compounds **1a**,[25] **1b-c**,[28] **1d**,[25] **1f-g**[28] were synthesized according to literature procedures.

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

25 Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721-7730.

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

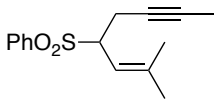
27 Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejović, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545-6547.

28 Escribano-Cuesta, A.; López-Carrillo, V.; Janssen, D.; Echavarren, A. M. *Chem. Eur. J.* **2009**, *15*, 5646-5650.

Preparation of Substrates

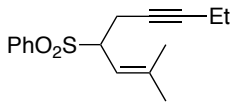
General procedure 1: synthesis of 3-phenylsulfonyl-1,5-enynes. Over a stirring solution of the allyl bromide (1M) in DMF sodium benzylsulfonate (1.5 equiv) was added at room temperature. The reaction mixture was stirred for 4-8 h. After extractive work-up (10% HCl solution and Et_2O) the corresponding allyl sulfone was isolated and used without further purification. A solution of the allylsulfone (1 equiv) in THF was cooled to -78 ºC and *n*-BuLi (1 equiv, 2.5 M in hexanes) was slowly added. After stirring for 20 minutes the corresponding propargyl bromide (1.5 equiv) was added. The reaction mixture was allowed to warm to room temperature and stirred for 6-10 h (^{1}H NMR monitoring).

(2-Methyloct-2-en-6-yn-4-ylsulfonyl)benzene (1b)



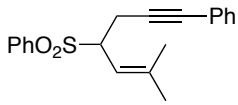
Compound **1b** was synthesized following the general procedure 1, starting from (3-methylbut-2-enylsulfonyl)benzene (799 mg, 3.42 mmol) in THF (20 mL) and 1-bromo-2-butyne (0.60 mL, 5.20 mmol). The residue was purified by column chromatography (hexane/EtOAc 8:1) to yield **1b** (535 mg, 60%) as a white solid: mp 83-84ºC; ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.84 (dm, J = 8.1 Hz, 2H), 7.62 (m, 1H), 7.52 (m, 1H), 5.05 (d, J =10.3 Hz, 1H), 3.89 (td, J = 10.3, 3.9 Hz, 1H), 2.90 (dm, J = 16.5 Hz, 1H), 2.59 – 2.51 (m,1H), 1.73 (d, J = 1.1 Hz, 3H), 1.69 (t, J = 2.5 Hz, 3H), 1.31 (d, J = 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8 (C), 137.7 (C), 133.5 (CH), 129.2 (CH), 128.7 (CH), 116.1 (CH), 78.2 (C), 73.8 (C), 63.7 (CH), 25.96 (CH_2), 19.2 (CH_3), 18.2 (CH_2); HRMS-ESI m/z calcd for $C_{15}H_{18}O_2NaS$ $[M+Na]^+$ 285.0925, found: 285.0938.

(2-Methylnon-2-en-6-yn-4-ylsulfonyl)benzene (1c)



1,5-Enyne **1c** was synthesized following the general procedure 1, starting from (3-methylbut-2-enylsulfonyl)benzene (500 mg, 2.14 mmol) in THF (10 mL), *n*-BuLi (0.8 equiv, 2.5 M in hexanes) and 1-bromo-2-pentyne (0.25 mL, 2.35 mmol). The residue was purified by automated flash chromatography (120 g RediSep flash column, hexane/EtOAc 20 min gradient 0-20% EtOAc) to yield **1c** (380 mg, 64%) as a white solid: mp 61-62ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.62 (m, 1H), 7.52 (m, 2H), 5.05 (dm, J = 10.7 Hz, 1H), 3.90 (dd, J = 3.7, 9.6 Hz, 1H), 2.92 (dm, J = 16.6 Hz, 1H), 2.55 (ddm, J = 9.6, 16.6 Hz, 1H), 2.09 – 2.02 (m, 2H), 1.72 (s, 3H), 1.32 (s, 3H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.63 (C), 137.7 (C), 133.5 (CH), 129.3 (CH), 128.7 (CH), 116.1 (CH), 84.3 (C), 74.1 (C), 63.8 (CH), 25.8 (CH_2), 19.1 (CH_2), 18.1 (CH_3), 13.9 (CH_3), 12.3 (CH_3); HRMS-ESI m/z calcd for $C_{16}H_{20}O_2NaS$ $[M+Na]^+$ 299.1082, found 299.1074.

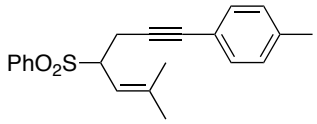
(6-Methyl-1-phenylhept-5-en-1-yn-4-ylsulfonyl)benzene (1d)



Enyne **1d** was synthesized by Sonogashira coupling of enyne **1a** and IPh. A mixture of $[Pd(PPh_3)_2Cl_2]$ (0.05 mol%), PhI (1.2 equiv), CuI (10 mol%), 1,5-enyne **1a** (294 mg, 1.18 mmol) and *i*-Pr_2NH (3 mL) was stirred at room temperature for 18 h. After extractive work-up (Et_2O) the residue was purified by column chromatography (8:1 hexane/EtOAc) to give **1d** (280 mg, 73%) as a yellow solid: mp 108-110ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dm, J = 7.6 Hz, 2H), 7.68 (m, 1H), 7.58 (m, 2H), 7.35 – 7.29 (m, 5H), 5.18 (dm, J = 10.4 Hz, 1H), 4.08 (td, J =10.2, 3.8 Hz, 1H), 3.25 (dd, J = 16.8, 3.8 Hz, 1H), 2.88 (dd, J = 16.8, 10.0Hz, 1H), 1.79 (d, J = 1.2 Hz, 3H),

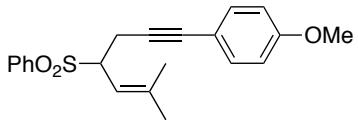
1.4 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0 (CH), 137.6 (C), 133.6 (C), 131.5 (CH), 129.2 (CH), 128.8 (CH), 128.1 (CH), 128.0 (CH), 123.2 (C), 116.0 (CH), 84.7 (C), 82.8 (C), 63.6 (CH), 25.9 (CH_2), 19.8 (CH_3), 18.2 (CH_3); HRMS-ESI m/z calcd for $C_{22}H_{20}O_2NaS$ $[M+Na]^+$ 347.1082, found 347.1091.

1-Methyl-4-(6-methyl-4-(phenylsulfonyl)hept-5-en-1-ynyl)benzene (1e)



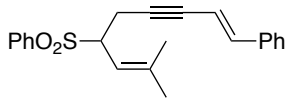
1,5-Enyne **1e** was synthesized by Sonogashira coupling of 1,5-enyne **1a** and *p*-iodotoluene. A mixture of $[Pd(PPh_3)_2Cl_2]$ (5 mol%), *p*-iodotoluene (1.2 equiv), CuI (10 mol%), 1,5-enyne **1a** (200 mg, 0.80 mmol) and Et_3N (4 mL) was stirred at room temperature for 16 h. The solvent was removed under vacuum and the crude was purified by flash chromatography (toluene 100%, then 5:1 hexane/EtOAc) to yield **1e** (160 mg, 59%) as a light yellow solid: mp 95-97ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.86 (m, 2H), 7.65 – 7.61 (m, 1H), 7.55 – 7.51 (m, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 5.13 (dquintuplet, J = 10.4, 1.4 Hz, 1H), 4.02 (td, J = 10.2, 3.8 Hz, 1H), 3.18 (dd, J = 16.8, 3.8 Hz, 1H), 2.38 (dd, J = 16.9, 9.9 Hz, 1H), 2.32 (s, 3H), 1.74 (d, J = 1.3 Hz, 3H), 1.35 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1 (C), 138.2 (C), 137.7 (C), 133.8 (CH), 131.5 (CH), 129.3 (CH), 129.1 (CH), 129.0 (CH), 120.2 (C), 116.2 (CH), 84.0 (C), 83.0 (C), 63.8 (CH), 26.1 (CH_3), 21.5 (CH_3), 20.0 (CH_3), 18.4 (CH_2); HRMS-ESI m/z calcd for C21H22NaO2S $[M+Na]^+$ 361.1238, found 361.1238.

1-Methoxy-4-(6-methyl-4-(phenylsulfonyl)hept-5-en-1-ynyl)benzene (1f)



1,5-Enyne **1f** was synthesized by Sonogashira coupling of 1,5-enyne **1a** and *p*-iodomethoxybenzene. A mixture of $[Pd(PPh_3)_2Cl_2]$ (5 mol%), *p*-iodomethoxybenzene (1.2 equiv), CuI (10 mol%), 1,5-enyne **1f** (200 mg, 0.805 mmol) and *i*-Pr_2NH (2 mL) was stirred at room temperature for 18 h. After extractive work-up (Et_2O) the residue was purified by flash chromatography (8:1 hexane/EtOAc) to yield **1f** (131 mg, 51%) as a light yellow solid: mp 127-129 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.1 Hz, 2H), 7.63 (m, 1H), 7.53 (m, 2H), 7.22 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 5.12 (dm, J = 10.1 Hz, 1H), 4.01 (dt, J = 4.0, 10.1 Hz, 1H), 3.78 (s, 3H), 3.17 (dd, J = 4.0, 16.9 Hz, 1H), 2.81 (dd, J = 10.1, 16.9 Hz, 1H), 1.74 (d, J = 1.0 Hz, 3H), 1.34 (d, J = 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9 (C), 137.6 (C), 133.6 (C), 132.9 (CH), 129.2 (CH), 128.8 (CH), 116.0 (CH), 115.3 (C), 113.8 (CH), 83.1 (C), 77.1 (C), 63.6 (CH), 55.2 (CH_3), 25.8 (CH_2), 19.8 (CH_3), 18.2 (CH_3); HRMS-ESI m/z calcd for $C_{21}H_{22}O_3NaS$ $[M+Na]^+$ 377.1187, found 377.1172.

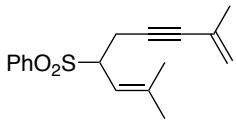
(*E*)-(8-Methyl-6-(phenylsulfonyl)nona-1,7-dien-3-yn-1-yl)benzene (1g)



1,5-Enyne **1h** was synthesized by Sonogashira coupling of 1,5-enyne **1a** and 2-bromo-1-propene. A mixture of $[Pd(PPh_3)_2Cl_2]$ (56.5 mg, 0.08 mmol), β-bromo-styrene (0.27 mL, 2.09 mmol), CuI (30.7 mg, 0.16 mmol), 1,5-enyne **1a** (400 mg, 1.61 mmol), *i*-Pr_2NH (6 mL) and CH_2Cl_2 (1 mL) was stirred at room temperature for 14 h. The solvent was removed under

vacuum and the crude was purified by flash chromatography (8:1 hexane/EtOAc) to yield **1h** (369 mg, 79%) as a sticky orange solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93- 7.76 (m, 2H), 7.74 – 7.60 (m, 1H), 7.60 – 7.51 (m, 2H), 7.37 – 7.22 (m, 5H), 6.79 (d, J = 16.2 Hz, 1H), 6.04 (dt, J = 16.2, 2.2 Hz, 1H), 5.10 (ddd, J = 5.3, 2.7, 1.3 Hz, 1H), 3.98 (td, J = 10.0, 3.9 Hz, 1H), 3.15 (ddd, J = 16.9, 3.9, 2.2 Hz, 1H), 2.81 (ddd, J = 16.9, 9.7, 2.2 Hz, 1H), 1.74 (d, J = 1.3 Hz, 3H), 1.34 (d, J = 1.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.2 (C), 141.1 (CH), 137.7 (C), 136.3 (C), 133.8 (CH), 129.4 (CH), 129.0 (CH), 128.8 (CH), 128.6 (C), 126.2 (CH), 116.1 (CH), 108.2 (CH), 87.1 (C), 82.2 (C), 63.6 (CH) 26.1 (CH_3), 20.1 (CH_2), 18.4 (CH_3); HRMS-ESI *m/z* calculated for $C_{22}H_{22}O_2SNa$ $[M+Na]^+$ 373.1238, found 373.1241.

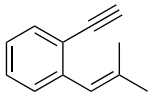
((2,8-Dimethylnona-2,8-dien-6-yn-4-yl)sulfonyl)benzene (1h)



1,5-Enyne **1i** was synthesized by Sonogashira coupling of 1,5-enyne **1a** and 2-bromo-1-propene. A mixture of $[Pd(PPh_3)_2Cl_2]$ (56.5 mg, 0.08 mmol), 2-bromo-1-propene (0.15 mL, 1.07 mmol), CuI (30.7 mg, 0.16 mmol), 1,5-enyne **1a** (400 mg, 1.61 mmol), $^{i}Pr_2NH$ (6 mL) and CH_2Cl_2 (1 mL) was stirred at room temperature for 14 h. The solvent was removed under vacuum and the crude was purified by flash chromatography (9:1 hexane/EtOAc) to yield **1i** (369 mg, 79%) as a sticky orange: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (m, 2H), 7.63 (m, 1H), 7.53 (m, 2H), 5.12 (s, 2H), 5.06 (d, J = 10.2 Hz, 1H), 3.94 (td, J = 10.2, 3.7 Hz, 1H), 3.07 (dd, J = 16.8, 3.7 Hz, 1H), 2.71 (dd, J = 16.8, 10.2 Hz, 1H), 1.77 (s, 3H), 1.72 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.0 (C), 137.7 (C), 133.8 (CH), 129.3 (CH), 129.0 (CH), 126.8 (C), 121.4 (CH_2), 116.1 (CH),

84.3 (C), 83.9 (C), 63.7 (CH), 26.0 (CH_3), 23.6 (CH_3), 19.8 (CH_2), 18.3 (CH_3); HRMS-ESI *m/z* calculated for $C_{17}H_{20}O_2SNa$ $[M+Na]^+$ 311.1080, found 311.1082.

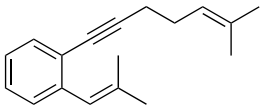
1-Ethynyl-2-(2-methylprop-1-enyl)benzene



1-Ethynyl-2-(2-methylprop-1-enyl)benzene was synthesized by Wittig reaction starting from 2-ethynylbenzaldehyde. To a solution of isopropyltriphenylphosphonium bromide (4.3 g, 9.88 mmol) in THF (19 mL) at 0 ºC was added *n*-BuLi (4.0 mL, 9.88 mmol). After 30 min. a solution of *o*-(2-trimethylsilylethynyl)benzaldehyde (2.0 g, 9.88 mmol) in THF (3 mL) was added and the mixture was stirred at room temperature for 4 h. The reaction was quenched with water and concentrated. After extractive work-up the residue was purified by column chromatography (hexane) to give 1-ethynyl-2-(2-methylprop-1-enyl)benzene (quantitative yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.5 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.15 (td, J = 7.4, 1.8 Hz, 1H), 6.49 (s, 1H), 3.25 (s, 1H), 1.94 (d, J = 1.0 Hz, 3H), 1.82 (d, J = 0.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1 (C), 137.0 (C), 132.8 (CH), 129.1 (CH), 128.2 (CH), 125.8 (CH), 123.6 (CH), 121.4 (C), 82.7 (C), 81.0 (CH), 26.6 (CH_3), 19.6 (CH_3).[29]

29 Madhushaw, R. J.; Lo, C.-Y.; Hwang, C.-W.; Su, M.-D.; Shen, H.-C.; Pal, S.; Shaikh, I. R.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, *126*, 15560-15565.

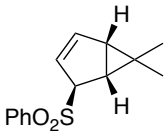
1-(6-Methylhept-5-en-1-ynyl)-2-(2-methylprop-1-enyl)benzene (8a)



To a solution of 1-ethynyl-2-(2-methylprop-1-enyl)benzene (400 mg, 2.54 mmol) in THF (2.5 mL) at -40 ºC was added *n*-BuLi (1.0 mL, 2.53 mmol). After 0.5 h HMPA (0.34 mL) was added followed by 5-bromo-2-methyl-2-pentene (0.34 mL, 2.54 mmol). The reaction mixture was heated to reflux overnight. The reaction was allowed to warm to room temperature and poured into ice water. After extractive work-up (Et_2O) the residue was purified by column chromatography (pentane/Et_2O 98:2) to give **8a** (0.4 g, 57%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (br d, J = 7.6 Hz, 1H), 7.25 – 7.19 (m, 2H), 7.11 (td, J = 7.5, 1.9 Hz, 1H), 6.48(s, 1H), 5.26 (m, 1H), 2.45 (t, J = 7.2 Hz, 2H), 2.30 (q, J = 7.1 Hz, 2H), 1.93 (d, J = 1.0 Hz, 3H), 1.82 (d, J = 0.8 Hz, 3H), 1.72 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3 (C), 136.0 (C), 132.9 (C), 132.1 (CH), 128.9 (CH), 127.0 (CH), 125.7 (CH), 124.2 (CH), 123.3 (C), 123.0 (CH), 94.4 (C), 79.7 (C), 27.7 (CH_2), 26.7 (CH_3), 25.7 (CH_3), 20.2 (CH_2), 19.6 (CH_3), 17.8 (CH_3); HRMS-AP$^+$ *m/z* calcd for $C_{18}H_{22}$ $[M + H]^+$ 239.1800, found 239.1792.

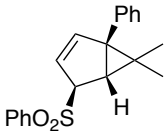
General procedure 2: cyclization of 1,5-enynes. The starting enyne was dried before the reaction by repeated evaporation of a solution of the compound in toluene (10 mg/mL, 3 times) under vacuum. A solution of the 1,5-enyne in CH_2Cl_2 (0.5 – 1 mL) was added to a solution of the gold(I) complex (5 mol%) in CH_2Cl_2 (0.5 mL) and stirred at room temperature until full conversion was reached (TLC monitoring). The crude reaction mixture was filtered through Celite® and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to provide the cyclized products.

(1*R,4*R**,5*S**)-6,6-Dimethyl-4-(phenylsulfonyl)bicyclo[3.1.0]hex-2-ene (2a)**



Compound **2a** was synthesized following general procedure 2, starting from **1a** (40.9 mg, 0.14 mmol) with catalyst **R**. The residue was purified by column chromatography (6:1 hexane/EtOAc) to give compound **2a** (35.8 mg, 88%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (m, 2H), 7.69 – 7.61 (m, 1H), 7.55 (m, 2H), 5.96 (dt, J = 5.5, 2.1, 1H), 5.64 – 5.55 (m, 1H), 3.87 (bs, 1H), 1.80 (d, J = 5.7, 1H), 1.71 – 1.64 (m, 1H), 1.11 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0 (CH), 136.9 (C), 133.5 (CH), 129.3 (CH), 128.6 (CH), 124.0 (CH), 71.5 (CH), 36.6 (CH), 28.9 (CH), 26.0 (CH), 23.9 (C), 13.2 (CH).

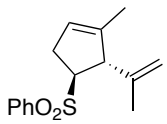
(1*R,4*S**,5*S**)-6,6-Dimethyl-1-phenyl-4-(phenylsulfonyl)bicyclo[3.1.0]hex-2-ene (2d)**



Compound **2d** was synthesized following general procedure 2, starting from **1d** (43.6 mg, 0.135 mmol) with catalyst **R**. The residue was purified by column chromatography (6:1 hexane/EtOAc) to give compound **2d** (21.8 mg, 50%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.92 (m, 2H), 7.67 (m, 1H), 7.60 – 7.52 (m, 2H), 7.17 (dd, J = 6.4, 3.7 Hz, 3H), 6.83 – 6.73 (m, 2H), 6.04 (dd, J = 5.4, 2.0 Hz, 1H), 5.65 (dt, J = 5.4, 1.8 Hz, 1H), 2.01 (s, 1H), 1.02 (s, 3H), 0.92 – 0.77 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5 (CH), 137.6 (C), 137.0 (C), 133.7 (CH), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.0 (CH), 126.5 (CH), 122.6 (CH), 71.8

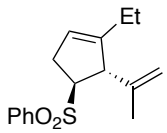
(CH), 50.5 (C), 33.3 (CH), 29.1 (C), 23.8 (CH_3), 14.9 (CH_3); HRMS-ESI *m/z* calcd for $C_{20}H_{20}O_2NaS$ $[M+Na]^+$ 347.1082, found 347.1084.

(1*R,2*R**)-3-Methyl-2-(prop-1-en-2-yl)cyclopent-3-enylsulfonylbenzene (3b)**



Compound **3b** was synthesized following general procedure 2, starting from **1b** (21.0 mg, 0.05 mmol) with catalyst **T** (3.4 mg, 0.003 mmol). The residue was purified by column chromatography (8:1 hexane/EtOAc) to give compound **3b** (17.2 mg, 80%) as an off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.74 (m, 2H), 7.69 – 7.59 (m, 1H), 7.58 – 7.50 (m, 2H), 5.41 – 5.31 (m, 1H), 4.66 (dd, *J* = 3.1, 1.5, 1H), 4.54 – 4.49 (m, 1H), 3.61 (dt, *J* = 9.2, 4.5, 1H), 3.55 (s, 1H), 2.98 – 2.79 (m, 1H), 2.76 – 2.55 (m, 1H), 1.56 – 1.50 (m, 3H), 1.48 (dd, *J* = 1.3, 0.8, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2 (C), 139.9 (C), 138.2 (C), 133.5 (CH), 129.0 (CH), 128.7 (CH), 123.3 (CH), 113.7 (CH_2), 66.9 (CH), 57.8 (CH), 32.8 (CH_2), 18.4 (CH_3), 14.5 (CH_3); HRMS-ESI *m/z* calcd for $C_{15}H_{18}O_2NaS$ $[M+Na]^+$ 285.0925, found 285.0919.

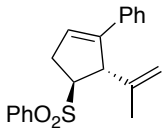
(((1*R,2*R**)-3-Ethyl-2-(prop-1-en-2-yl)cyclopent-3-en-1-yl)sulfonyl)benzene (3c)**



Compound **3c** was synthesized following general procedure 2, starting from **1c** (59.5 mg, 0.22 mmol) with catalyst **T** (9.3 mg, 0.008 mmol). The residue

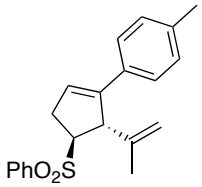
was purified by column chromatography (8:1 hexane/EtOAc) to give compound **3c** (42.8 mg, 72%) as a off-white sticky solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (m, 2H), 7.63 (m, 1H), 7.54 (m, 2H), 5.34 (d, J = 1.7 Hz, 1H), 4.71 – 4.62 (m, 1H), 4.53 (s, 1H), 3.62 (m, 1H), 2.90 (d, J = 17.6 Hz, 1H), 2.80 – 2.57 (m, 1H), 1.95 – 1.84 (m, 1H), 1.83 – 1.71 (m, 1H), 1.49 (s, 3H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2 (C), 143.7 (C), 138.4 (C), 133.7 (CH), 129.2 (CH), 128.9 (CH), 121.3 (CH), 113.9 (CH), 67.1 (CH), 56.9 (CH), 32.9 (CH_2), 22.1 (CH_2), 18.7 (CH_3), 11.9 (CH_3).

(((1*R,2*R**)-3-Phenyl-2-(prop-1-en-2-yl)cyclopent-3-en-1-yl)sulfonyl)benzene (3d)**



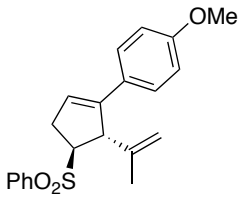
Compound **3d** was synthesized following general procedure 2, starting from **1d** (40.9 mg, 0.12 mmol) with catalyst **T** (8.6 mg, 0.007 mmol). The residue was purified by column chromatography (8:1 hexane/EtOAc) to give compound **3d** (27.1 mg, 67%) as an off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dt, J = 8.5, 1.8 Hz, 2H), 7.62 (ddd, J = 6.7, 3.9, 1.3 Hz, 1H), 7.58 – 7.46 (m, 2H), 7.36 – 7.12 (m, 5H), 6.06 (d, J = 0.7 Hz, 1H), 4.78 – 4.65 (m, 1H), 4.58 (d, J = 0.7 Hz, 1H), 4.19 (s, 1H), 3.65 (dt, J = 9.2, 3.3 Hz, 1H), 3.08 (dt, J = 18.8, 3.1 Hz, 1H), 2.88 (ddt, J = 18.8, 9.2, 2.3 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0 (C), 142.7 (C), 137.9 (C), 134.7 (C), 133.8 (CH), 129.3 (CH), 129.1 (CH), 128.4 (CH), 127.7 (CH), 126.2 (CH), 124.8 (CH), 114.0 (CH), 68.2 (CH), 54.8 (CH), 33.3 (CH_2), 19.7 (CH_3); HRMS-ESI *m/z* calcd for $C_{20}H_{20}O_2NaS$ $[M+Na]^+$ 347.1082, found 347.1095.

(1*R,2*R**)-1-Methyl-4-(4-(phenylsulfonyl)-5-(prop-1-en-2-yl)cyclopent-1-en-1-yl)benzene (3e)**



Compound **3e** was synthesized following general procedure 2, starting from **1e** (56.5 mg, 0.17 mmol) with catalyst **T** (10.1 mg, 0.008 mmol). The residue was purified by column chromatography (8:1 hexane/EtOAc) to give compound **3e** (32.8 mg, 58%) as a dark yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (m, 2H), 7.67 – 7.58 (m, 1H), 7.53 (m, 2H), 7.19 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 5.99 (d, J = 2.8 Hz, 1H), 4.77 – 4.63 (m, 1H), 4.58 (s, 1H), 4.17 (s, 1H), 3.64 (dt, J = 9.2, 3.3 Hz, 1H), 3.06 (dt, J = 18.7, 3.1 Hz, 1H), 2.87 (ddt, J = 18.8, 9.2, 2.3 Hz, 1H), 2.30 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.12 (C), 142.53 (C), 137.89 (C), 137.52 (C), 133.81 (CH), 131.94 (C), 129.25 (CH), 129.05 (CH), 128.3 (CH), 126.11 (CH), 123.83 (CH), 113.90 (CH_2), 68.19 (CH), 54.82 (CH), 33.28 (CH_2), 21.30 (CH_3), 19.63 (CH_3); HRMS-ESI *m/z* calcd for $C_{15}H_{18}O_2NaS$ $[M+Na]^+$ 285.0925, found 285.0919.

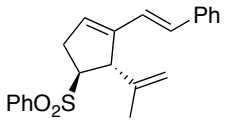
(1*R,2*R**)-1-Methoxy-4-(4-(phenylsulfonyl)-5-(prop-1-en-2-yl)cyclopent-1-en-1-yl)benzene (3f)**



Compound **3f** was synthesized following general procedure 2, starting from **1f** (40.5 mg, 0.11 mmol) with catalyst **T** (7.2 mg, 0.006 mmol). The residue

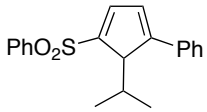
was purified by column chromatography (8:1 hexane/EtOAc) to give compound **3f** (23.6 mg, 58%) as a orange solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.85 (m, 2H), 7.70 – 7.60 (m, 1H), 7.56 (t, J = 7.6 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 5.95 (s, 1H), 4.80 – 4.67 (m, 1H), 4.60 (s, 1H), 4.17 (d, J = 1.8 Hz, 1H), 3.80 (s, 3H), 3.65 (dd, J = 6.2, 2.9 Hz, 1H), 3.08 (dt, J = 18.7, 3.1 Hz, 1H), 2.88 (ddt, J = 18.7, 9.2, 2.3 Hz, 1H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (C), 144.2 (C), 142.0 (C), 137.9 (C), 133.8 (CH), 129.2 (CH), 129.0 (CH), 127.5 (C), 127.4 (CH), 122.7 (CH), 113.9 (CH), 113.7 (CH_2), 68.2 (CH), 55.3 (CH_3), 54.9 (CH), 33.3 (CH_2), 19.6 (CH_3); HRMS-ESI *m/z* calcd for $C_{21}H_{22}O_3NaS$ $[M+Na]^+$ 377.1187, found 377.1198.

((*E*)-2-((4*R,5*R**)-4-(Phenylsulfonyl)-5-(prop-1-en-2-yl)cyclopent-1-en-1-yl)vinyl)benzene (3g)**



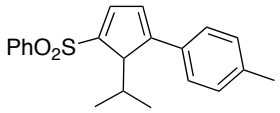
Compound **3g** was synthesized following general procedure 2, starting from **1g** (66.0 mg, 0.02 mmol) with catalyst **H** (7.3 mg, 9.42 μmol) stirred under microwave irradiation (Biotage Initiator^{TM} 2.0) at 100 ºC for 45 min. The residue was purified by column chromatography (8:1 hexane/EtOAc) to give **3g** (13.2 mg, 20%) as a sticky yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 – 7.89 (m, 2H), 7.64 (m, 1H), 7.55 (m, 2H), 7.32 (m, 5H), 6.73 (d, J = 16.4 Hz, 1H), 6.47 (d, J = 16.2 Hz, 1H), 5.79 (s, 1H), 5.24 – 5.12 (m, 1H), 4.72 (t, J = 1.4, 1H), 4.59 (s, 1H), 4.03 (s, 1H), 3.58 (dt, J = 9.2, 3.2 Hz, 1H), 3.03 (dt, J = 6.2, 3.3 Hz, 1H), 2.85 (dd, J = 19.9, 8.8 Hz, 1H), 1.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 144.3 (C), 141.9 (C), 137.3 (C), 133.9 (CH), 130.5 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 128.7 (CH), 127.8 (CH), 126.5 (CH), 123.4 (CH), 113.6 (CH_2), 68.3 (CH), 56.3 (C), 53.9 (CH), 33.2 (CH_2), 19.3 (CH_3); HRMS-ESI *m/z* calcd for $C_{22}H_{22}O_2SNa$ $[M+Na]^+$ 373.1238, found 373.1234.

(5-Isopropyl-4-(phenylsulfonyl)cyclopenta-1,3-dien-1-yl)benzene (4d)



Compound **4d** was synthesized following general procedure 2, starting from **1d** (40.9 mg, 0.12 mmol) with catalyst **T** (8.6 mg, 0.007 mmol). The residue was purified by column chromatography (8:1 hexane/EtOAc) to give compound **4d** as a mixture of tautomers (10.2 mg, 25%) as a dark orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.96 (m, 2H), 7.66 – 7.53 (m, 3H), 7.40 – 7.30 (m, 6H), 6.56 (d, J = 2.4 Hz, 1H), 3.92 (s, 1H), 2.47 (dseptuplet, J = 7.0, 2.6 Hz, 1H), 0.75 (d, J = 7.0 Hz, 3H), 0.69 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0 (C), 146.3 (C), 144.3 (CH), 141.6 (C), 136.0 (C), 133.1 (CH), 129.2 (CH), 128.7 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 126.6 (CH), 59.1 (CH), 29.5 (CH), 19.1 (CH_3), 18.2 (CH_3); HRMS-ESI *m/z* calcd for $C_{20}H_{20}O_2NaS$ $[M+Na]^+$ 347.1082, found 347.1098.

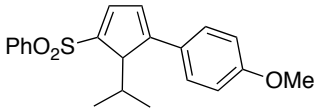
1-(5-Isopropyl-4-(phenylsulfonyl)cyclopenta-1,3-dien-1-yl)-4-methylbenzene (4e)



Compound **4e** was synthesized following general procedure 2, starting from **1e** (56.5 mg, 0.17 mmol) with catalyst **T** (10.1 mg, 0.008 mmol). The residue was purified by column chromatography (8:1 hexane/EtOAc) to give compound **1e** (11.6 mg, 21%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.92 (m, 2H), 7.59 – 7.50 (m, 3H), 7.32 (ddd, J = 2.6, 1.5, 0.5 Hz, 1H), 7.20 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 6.50 (d, J = 2.5 Hz, 1H), 3.86 (m, 1H), 2.42 (dseptuplet, J = 7.0, 2.6 Hz, 1H), 2.38 – 2.27 (m, 3H), 0.74 (d, J = 7.0 Hz, 3H), 0.66 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (C), 145.7 (C), 144.5 (CH), 141.7 (C), 138.7

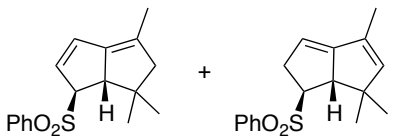
(C), 133.2 (C), 133.1 (CH), 129.4 (CH), 129.2 (CH), 127.9 (CH), 127.8 (CH), 125.8 (CH), 58.9 (CH), 29.6 (CH), 21.4 (CH_3), 18.9 (CH_3), 18.4 (CH_3); HRMS-ESI *m/z* calculated for $C_{21}H_{22}O_2SNa$ $[M+Na]^+$ 361.1238, found 361.1253

1-(5-isopropyl-4-(phenylsulfonyl)cyclopenta-1,3-dien-1-yl)-4-methoxybenzene (4f)



Compound **4f** was synthesized following general procedure 2, starting from **1f** (40.5 mg, 0.11 mmol) with catalyst **T** (7.2 mg, 0.006 mmol). The residue was purified by column chromatography (8:1 hexane/EtOAc) to give compound **4f** (11.3 mg, 28%) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.61 – 7.53 (m, 4H), 7.35 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 6.48 (d, *J* = 2.5 Hz, 1H), 3.86 (s, 1H), 3.84 (s, 3H), 2.43 (dseptuplet, *J* = 2.5, 7.0 Hz, 1H), 0.78 (d, *J* = 7.0 Hz, 3H), 0.68 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (C), 159.9 (C), 145.1 (C), 144.7 (CH), 141.7 (C), 133.0 (CH), 129.2 (CH), 129.2 (CH), 128.6 (C), 127.9 (CH), 125.0 (CH), 114.1 (CH), 58.9 (CH), 55.5 (CH_3), 29.8 (CH), 18.8 (CH_3), 18.5 (CH_3).

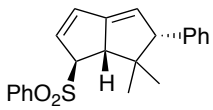
(6*R,6a*R**)-1,1,3-Trimethyl-6-(phenylsulfonyl)-1,2,6,6a-tetrahydropentalene (5b) and (1*R**,6a*R**)-4,6,6-trimethyl-1-(phenylsulfonyl)-1,2,6,6a-tetrahydropentalene (5b')**



Compounds **5b** and **5b'** were synthesized following general procedure 2, starting from **1i** (75.6 mg, 0,26 mmol) with catalyst **R** (12.2 mg, 0.013 mmol). The residue was purified by column chromatography (8:1

hexane/EtOAc) to give a 1.5:1 mixture of isomers **5b** and **5b'** (33.6 mg, 44%) as a yellow oil: Major isomer **5b** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 – 7.80 (m, 2H), 7.72 – 7.61 (m, 1H), 7.61 – 7.50 (m, 2H), 6.36 (dd, J = 5.6, 2.3 Hz, 1H), 5.90 (d, J = 5.1 Hz, 1H), 4.36 (d, J = 6.7 Hz, 1H), 3.33 – 3.22 (m, 1H), 2.72 – 2.60 (m, 1H), 2.03 (d, J = 15.9 Hz, 1H), 1.65 (s, 3H), 1.06 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.3 (C), 137.7 (C), 133.8 (CH), 131.5 (CH), 130.9 (CH), 129.4 (CH) 129.1 (CH), 128.2 (C), 70.2 (CH), 60.1 (CH), 58.0 (CH_2), 43.0 (C), 27.1 (CH_3), 24.2 (CH_3), 15.3 (CH_3). Minor isomer **5b'** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 – 7.80 (m, 2H), 7.72 – 7.61 (m, 1H), 7.61 – 7.50 (m, 2H), 5.63 (br, 1H), 5.06 (dd, J = 5.0, 3.0 Hz, 1H), 3.75 – 3.69 (m, 1H), 3.42 (ddd, J = 10.4, 4.6, 2.9 Hz, 1H), 3.11 (dd, J = 15.8, 9.6 Hz, 1H), 2.72 – 2.60 (m, 1H), 1.71 (d, J = 1.3 Hz, 3H), 1.19 (s, 3H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.2 (C), 149.2 (CH), 134.7 (C), 133.7 (CH), 132.2 (C), 129.3 (CH), 128.9 (CH), 108.9 (CH), 65.7 (CH), 59.6 (CH), 42.7 (C), 39.9 (CH_2), 27.6 (CH_3), 22.5 (CH_3), 12.9 (CH_3); HRMS-ESI *m/z* calculated for $C_{17}H_{20}O_2SNa$ $[M+Na]^+$ 311.1096, found 311.1082.

(2*R,6*R**,6a*R**)-1,1-Dimethyl-2-phenyl-6-(phenylsulfonyl)-1,2,6,6a-tetrahydropentalene (5a)**



Compound **5a** was synthesized following general procedure 2, starting from **1h** (66.0 mg, 0.188 mmol) with catalyst **H** (7.3 mg, 9.42 µmol) stirred under microwave irradiation (Biotage Initiator^{TM} 2.0) at 100 ºC for 45 min. The residue was purified by column chromatography (8:1 hexane/EtOAc) to give **5a** (26.4 mg, 40%) as a sticky yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 – 7.86 (m, 2H), 7.71 – 7.63 (m, 1H), 7.63 – 7.54 (m, 2H), 7.34 – 7.19 (m, 3H), 7.13 – 7.07 (m, 2H), 6.48 (dd, J = 5.6, 2.3 Hz, 1H), 6.08 (d, J = 5.6 Hz, 1H), 5.58 – 5.54 (m, 1H), 4.41 – 4.37 (m, 1H), 4.04 –

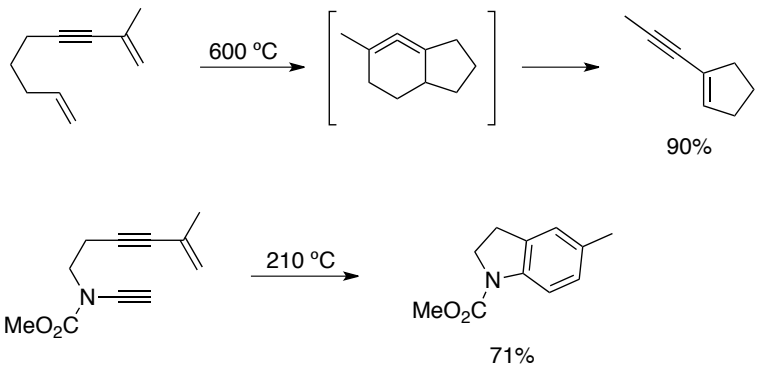
4.02 (m, 1H), 3.42 (dt, J = 6.2, 3.1 Hz, 1H), 1.11 (s, 3H), 0.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.4 (C), 140.0 (C), 137.5 (C), 134.0 (CH), 133.8 (CH), 132.7 (CH), 129.4 (CH), 129.3 (CH), 128.9 (CH), 128.1 (CH), 126.8 (CH), 121.1 (CH), 70.3 (CH), 66.6 (CH), 60.8 (CH), 50.9 (C), 25.4 (CH_3), 18.8 (CH_3); HRMS-ESI *m/z* calculated for $C_{22}H_{22}O_2SNa$ $[M+Na]^+$ 373.1238, found 373.1247.

Chapter 2. Gold(I)-Catalyzed Cycloaddition of 1,5-Benzylenynes

2.1. Introduction

Construction of bicyclic and tricyclic systems is of importance for the practical synthesis of many bioactive compounds. Metal-catalyzed cycloaddition reactions are a powerful tool for the preparation of these cyclic carbon skeletal structures.[1]

[4+2] Cycloaddition reaction of enynes, diynes, and dienynes is a well-know pericyclic reaction between two or more unsaturated molecules (or parts of the same molecule) via cyclic intermediates. The thermal transformation requires high temperatures (*Scheme 1*).[2]

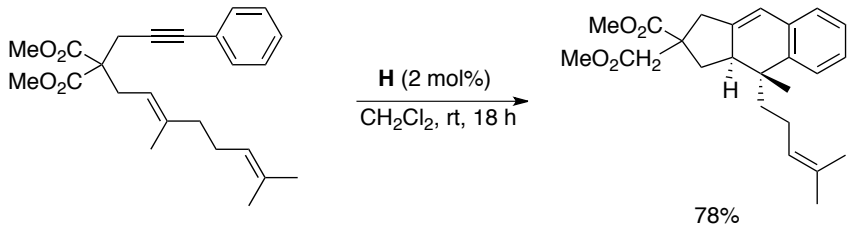


Scheme 1. Thermal [4 + 2] cycloaddition reaction.

1 Lee, S. I.; Park, S. Y.; Chung, Y. K. *Adv. Synth. Catal.* **2006**, *348*, 2531-2539.

2 (a) Burrell, R. C.; Daoust, K. J.; Bradley, A. Z.; DiRico, K. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1996**, *118*, 4218-4219. (b) Coudanne, I.; Balme, G. *Synlett* **1998**, 998-1000. (c) Danheiser, R. L.; Gould, A. E.; de la Pradilla, R. F.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514-5515. (d) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776-5777.

Several, examples of gold(I)-catalyzed [4+2] cycloaddition reaction have been described.[3] Thus, 1,6-enynes substituted at the alkyne with an aryl group react stereospecifically with gold catalysts to provide tricyclic products resulting from a formal intramolecular [4+2] cycloaddition (*Scheme 2*).[3b]

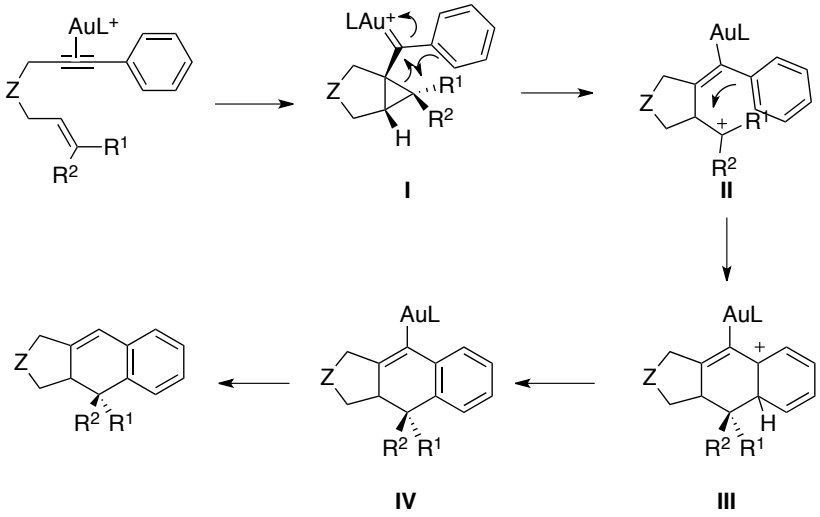


Scheme 2. Intramolecular [4+2] cycloaddition of 1,6-arylenynes.

This reaction occurs under very mild conditions and tolerates both electron donating and electron withdrawing substituents at several positions of the arene. According to DFT calculations, this transformation proceeds stepwise by an initial *exo*-cyclization via intermediates of type **I** (***Scheme 3***). Opening of the cyclopropyl gold(I) carbene to form a carbocation stabilized by a π interaction with the aryl ring followed by a Friedel-Crafts-type reaction giving **III**. After, aromatization to form alkenyl gold intermediate **IV** followed by proto-demetalation leads to the expected tricyclic product.

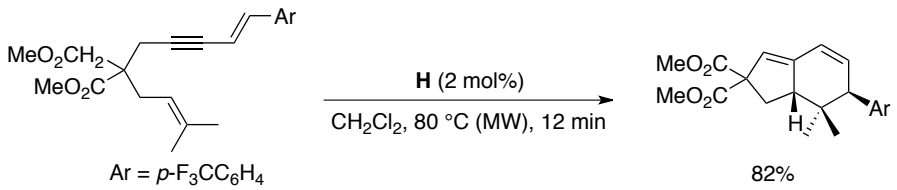
3 (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148. (b) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269-279.

(c) Yeh, M.-C. P.; Tsao, W.-C.; Lee, B.-J.; Lin, T.-L. *Organometallics* **2008**, *27*, 5326-5332. (d) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133-4136. (e) Chao, C.-M.; Vitale, M. R.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Chem. Eur. J.* **2009**, *15*, 1319-1323.



Scheme 3. Mechanism for the [4+2] cycloaddition of arylenines.

Aryl substituents stabilize the gold carbene intermediates resulting in higher energy barriers limiting the possibility for a skeletal rearrangement. In a similar mechanism, enynes bearing an alkene substituent in the alkyne moiety give hyndrindanes stereoselectively (*Scheme* 6).[3b] In addition, aryl-substituted enynes in the presence of strong Brönsted acid give rise to different cyclization processes initiated by protonation of the alkene.[4]



Scheme 4. Cyclization of dienynes catalyzed by gold(I) to give hyndrindanes.

4 Jin, T.; Himuro, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2010**, *132*, 5590-5591.

Related cyclizations of allenes with alkynes[5,6] and diynes[7,8] have been described. The *endo*-cyclization also takes place as a minor pathway in certain cases,[3b] which happens to be the major pathway in the platinum(II)- or gold(I)-catalyzed cycloaddition of related arylalkynes with enesulfonamides or enamines. [9,10 11,]

An alternative mechanism has been proposed when 1,3-dien-8-ynes are used resulting in an intramolecular Diels-Alder. [12 , 13] Although cyclization of 1,3-dien-8-ynes with $AuCl_3$ gives the product of formal [4+2] cycloaddition (*Scheme 5*), $Au(PPh_3)Cl$ leads a hexahydropentalene.

5 Lemière, G.; Gandon, V.; Agenet, N.; Goddard, J.-P.; de Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 7596-7599.

6 Lin, G.-Y.; Yang, C.-Y.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 6753-6757.

7 Lian, J.-J.; Chen, P.-C.; Lin, Y.-P.; Ting, H.-C.; Liu, R. S. *J. Am. Chem. Soc.* **2006**, *128*, 11372-11373.

8 Shibata, T.; Fujiwara, R.; Takano, D. *Synlett* **2005**, 2062-2066. Erratum: *Synlett* **2007**, 2766.

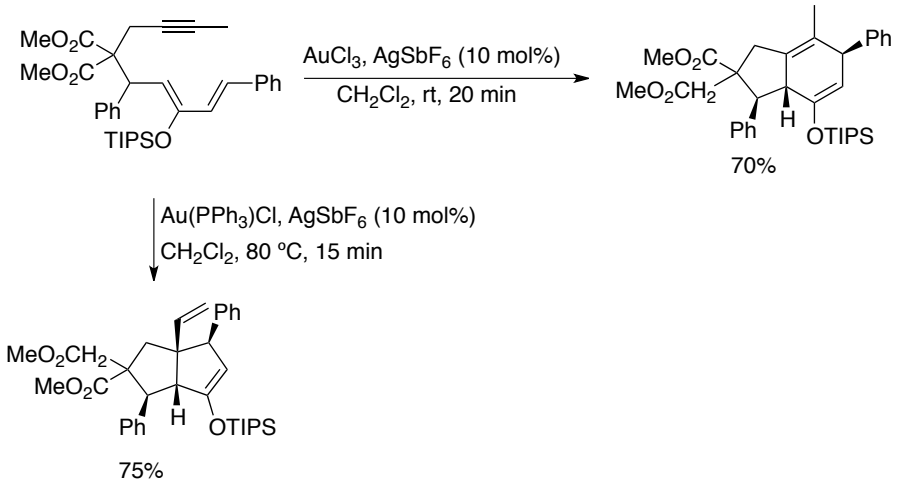
9 Kozak, J. A.; Dodd, J. M.; Harrison, T. J.; Jardine, K. J.; Patrick, B. O.; Dake, G. R. *J. Org. Chem.* **2009**, *74*, 6929-6935.

10 Kozak, J. A.; Patrick, B. O.; Dake, G. R. *J. Org. Chem.* **2010**, *75*, 8585-8590.

11 Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367-370.

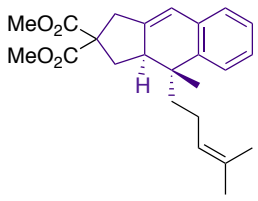
12 Fürstner, A.; Stimson, C. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 8845-8849.

13 Kusama, H.; Karibe, Y.; Onizawa, Y.; Iwasawa, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 4269-4272.

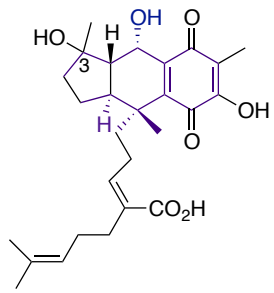


Scheme 5. Behavior of 1,3-dien-8-yne with two different gold(I)-catalysts.

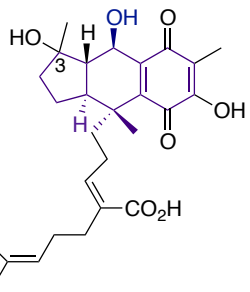
Gold(I)-catalyzed intramolecular [4+2] cycloaddition of arylalkynes to give tricyclic products is of particular interest as pycnanthuquinones A, B and C have the carbon skeleton of these tricyclic compounds.



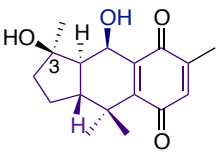
[4+2] cycloaddition product



pycnanthuquinone A



pycnanthuquinone B



pycnanthuquinone C

Figure 1. Structures of pycnanthuquinones A, B, C.

Pycnanthuquinone A and B were isolated from leaves and stems of the Africant plant, *Pycnanthus angolensis* Warb (a tree that grows in West and Central Africa) by bioassay-guided fractionation of an ethanolic extract using a diabetic mouse model (*Figure 2*a).[14] This plant was selected because its leaves, twigs, seed fat, and bark exudate are used to treat oral thrush, fungal skin infections and body aches. These are common symptoms for persons suffering from type 2 diabetes mellitus (syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels). A test with using a db/db mouse model for type 2 diabetes revealed that these novel terpenoid-quinone structures are potentially new drugs for the treatment of this disease.

a) ***b)***

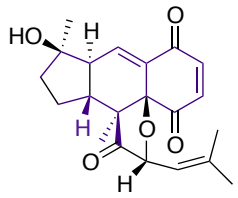
Figure 2. a) *Pycnanthus angolensis Warb*. b) *Cysotsphora harveyi*.

Posterior chemical investigation of the Western Australian marine brown algae *Cystosphora harveyi* (*Figure 2*b) resulted in the isolation of a new linearly fused 6,6,5-tricyclic compound known as pycnanthuquinone C

14 Fort, D. M.; Ubillas, R. P.; Mendez, C. D.; Jolad, S. D.; Inman, W. D.; Carney, J. R.; Chen, J. L.; Ianiro, T. T.; Hasbun, C.; Bruening, R. C.; Luo, J.; Reed, M. J.; Iwu, M.; Carlson, T. J.; King, S. R.; Bierer, D. E.; Cooper, R. *J. Org. Chem.* **2000**, *65*, 6534-6539.

(*Figure 1*)[15] which possesses a similar backbone to pycnanthuquinone A and B.

The configuration of both pycnanthuquinones was determined by NMR spectroscopy allowing the assignment of the ring junction as *trans* and the relative configuration at C-1 and C-2. In addition, molecular modeling experiments suggested the relative configuration at C-3 as the most probable one but NOE experiments were not conclusive. Moreover, rossinone B,[16] a biologically active meroterpene from an Antarctic Ascidian Aplidium species, was isolated and characterized with spectroscopic methods determining its configuration. This allowed to assign the configuration of pycnanthuquinones.



rossinone B

Figure 3. Structure of rossinone B.

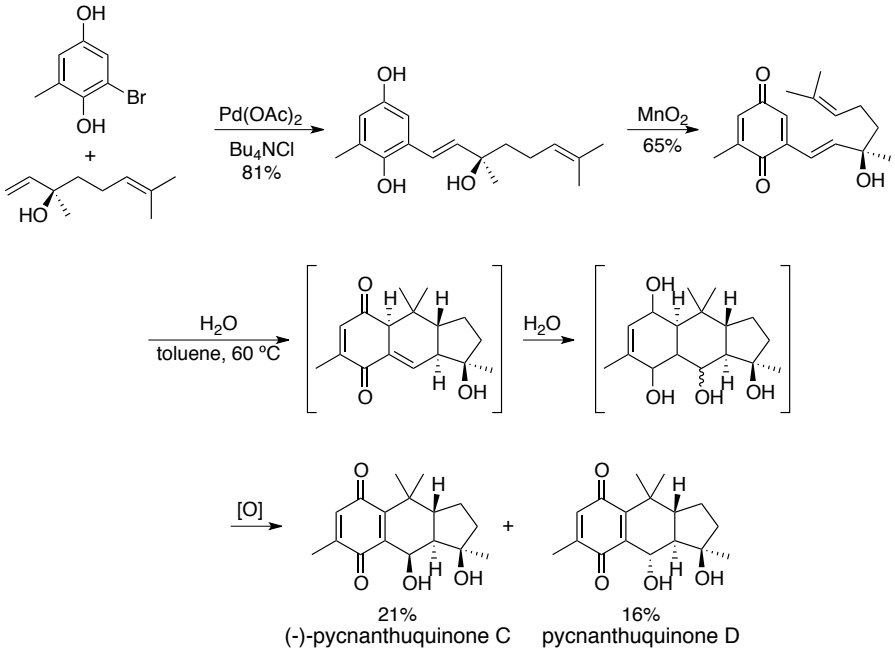
Due to the importance of these biologically active terpenoids and the structure of their carbon skeleton, we were interested in applying the [4+2] intramolecular cycloaddition reaction for the synthesis of the pycnanthuquinones, particularly pycnanthuquinone C.

Recently, the group of Trauner reported the first synthesis of the natural enantiomer of pycnanthuquinone C providing the full elucidation of

15 Laird, D. W.; Poole, R.; Wikström, M.; van Altena, I. A. *J. Nat. Prod.* **2007**, *70*, 671-674.

16 Appleton, D. R.; Chuen, C. S.; Berridge, M. V.; Webb, V. L.; Copp, B. R. *J. Org. Chem.* **2009**, *74*, 9195-9198.

its configuration.[17] This biomimetic synthesis consists of a three step procedure through a Diels-Alder reaction of a vinyl quinone (*Scheme 6*). The last step of this synthesis provided (-)-pycananthuquinone C and its epimer, which was named pycnanthuquinone D, in moderate overall yield.



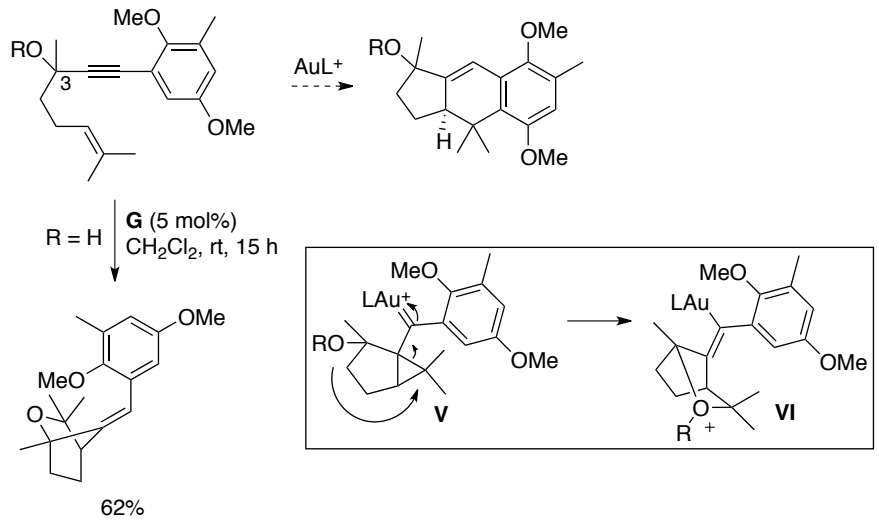
Scheme 6. Biomimetic synthesis of (-)-pycnanthuquinone C and pycnanthuquinone D.

In a first attempt to synthesize pycnanthuquinone C applying the intramolecular [4+2] cycloaddition reaction, three strategies were proposed differing on the substitution at C-3.[18] *Route 1* will lead to the most functionalized cyclization product. However, an unexpected product was obtained consistent with the mechanism shown in *Scheme 7*.

17 Löbermann, F.; Mayer, P.; Trauner, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 6199-6202.

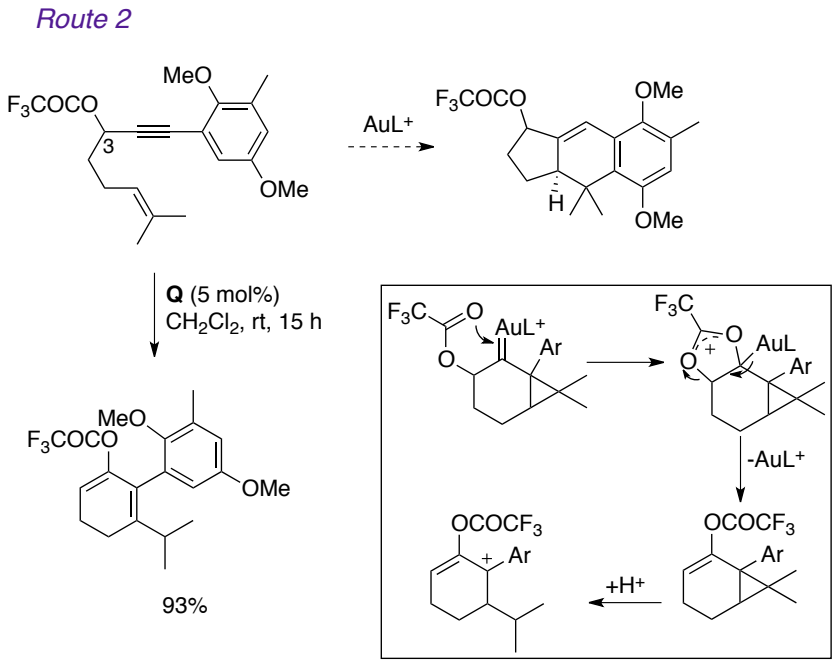
18 Pérez-Galán, P.; Lauterbach, T. Unpublished results. ICIQ. Tarragona 2007-2008.

Route 1



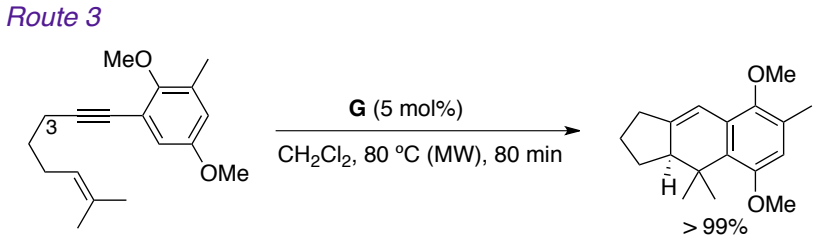
Scheme 7. Route 1: toward the synthesis of pycnanthuquinone C.

Route 2 offers a highly functionalized intermediate (*Scheme 8*). However, in this case the reaction takes place via a 6-*endo-dig* cyclization with migration of the OR group leading to the undesired 1,3-diene as product.



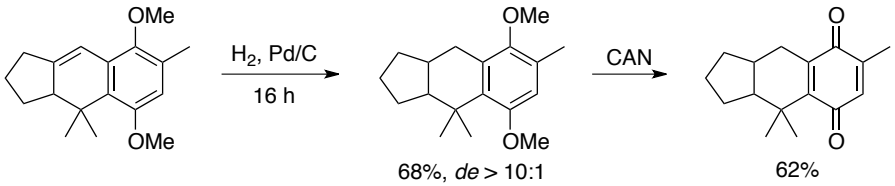
Scheme 8. Route 2: toward the synthesis of pycnanthuquinone C.

Finally, *route 3* bearing no functional groups at C-3 was also examined (*Scheme 9*).[18] As the precursor does not contain a stereogenic center an enantioselective synthesis would require the use of a chiral gold catalyst. The cyclization was achieved successfully in quantitative yield giving the product of the [4+2] cycloaddition reaction strereospecifically. This reaction was performed reproducibly in up to 2.0 g scale under microwave irradiation.



Scheme 9. Route 3: toward the synthesis of pycnanthuquinone C.

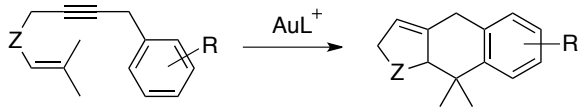
Different studies were done with the objective to functionalize the tricyclic precursor toward the synthesis of pycnanthuquinone C. Firstly epoxidation of the double bond was attempted under several conditions. Unfortunately, the desired epoxide could not be obtained. Similarly, all attempts to functionalize this position by different allylic oxidation procedures, failed to give the desired compound. Finally, hydrogenation of the double bond was assayed successfully followed by oxidation with CAN to afford a quinone adduct with the skeleton of the pycnanthuquinone C (*Scheme 10*).



Scheme 10. Preparation of a model for the synthesis of the pycnanthuquinone C.

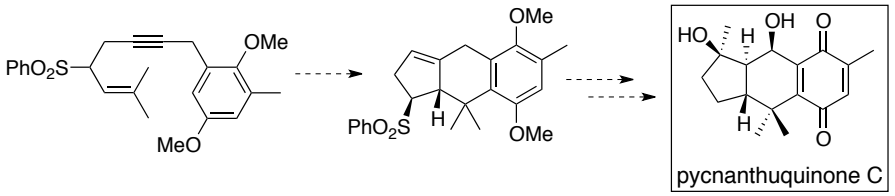
2.2. *Objectives*

Gold(I)-catalyzed intramolecular [4+2] cycloaddition reaction of alkenyl or aryl substituted 1,6-enynes was studied recently in detail.[3a,6b] We decided to develop a new gold-catalyzed cyclization reaction of benzyl-substituted 1,5-enynes as a general method for the synthesis of new tricyclic products (*Scheme 11*).



Scheme 11. Gold-catalyzed cyclization of 1,5-benzylenynes.

Considering all the results obtained previously toward the synthesis pycnanthuquinone C and with the purpose of achieving the total synthesis of this novel natural product, we decided to apply the cyclization reaction of 1,5-benzylenynes as the key step of its synthesis.



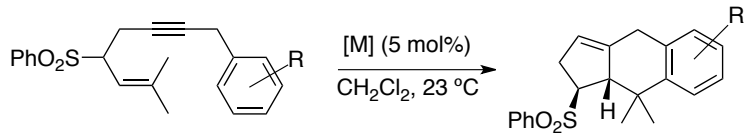
Scheme 12. Application of 1,5-benzylenyne cyclization methodology to the synthesis of pycnanthuquinone C.

2.3. Results and Discussion

2.3.1. Intramolecular cycloaddition reaction of 1,5-benzylenyes

1,6-Enynes bearing alkenyl or aryl groups at the alkyne react to give hydrindanes or linearly fused tricyclic systems in a formal [4+2] cycloaddition reaction (*Scheme 4*).[3b] In this work, we decided to study the intramolecular cycloaddition reaction of 1,5-benzylenynes[19] reminiscent to the formal [4+2] cycloaddition of aryl-substituted 1,6-enynes. This reaction is catalyzed by different Au(I) complexes achieving better results when gold(I) is coordinated to phosphine or phosphite ligands (***Table 1***).

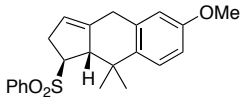
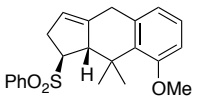
Table 1. Metal-catalyzed cyclization of 1,5-benzylenynes.

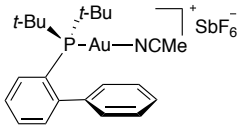


1a-e **2a-e**

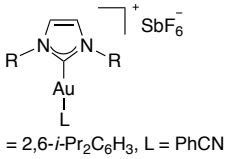
entry	R (enyne)	[M]	time (h)	product (yield %)
1	H (**1a**)	**H**	14	**2a** (95)
2	H (**1a**)	**T**	12	**2a** (71)
3	*p*-OMe (**1b**)	**R**	3	**2b** (66)
4	*p*-OMe (**1b**)	**H**	3	**2b** (66)
5	*p*-OMe (**1b**)	**T**	2	**2b** (95)
6	*p*-OMe (**1b**)	$PtCl_4$	16	**2b** (34)
7	*p*-OMe (**1b**)	**W**	16	**2b** (38)
8	*p*-Ph (**1c**)	**R**	14	**2c** (63)
9	*p*-Ph (**1c**)	**H**	14	**2c** (60)

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

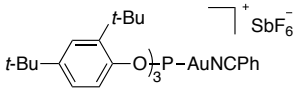
10	*p*-Ph (**1c**)	**T**	0.2	**2c** (92)
11	2,3,4-(OMe)$_3$ (**1d**)	**H**	14	**2d** (64)
12	2,3,4-(OMe)$_3$ (**1d**)	**T**	0.2	**2d** (45)
13	*m*-OMe (**1e**)	**H**	14	 **2e** (55)  **2e'** (12)
14	*m*-OMe (**1e**)	**T**	14	**2e** (57) + **2e'** (31)



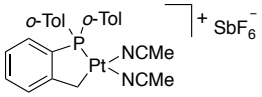
H



R: R = 2,6-*i*-Pr$_2$C$_6$H$_3$, L = PhCN



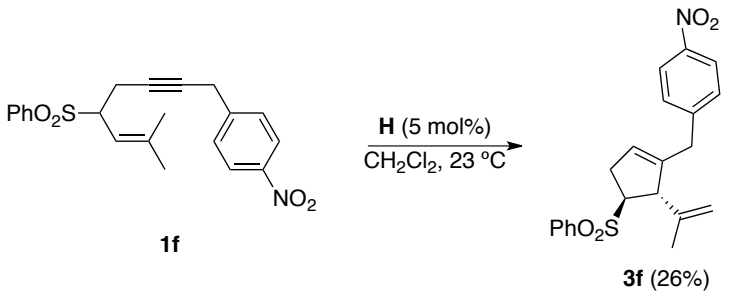
T



W

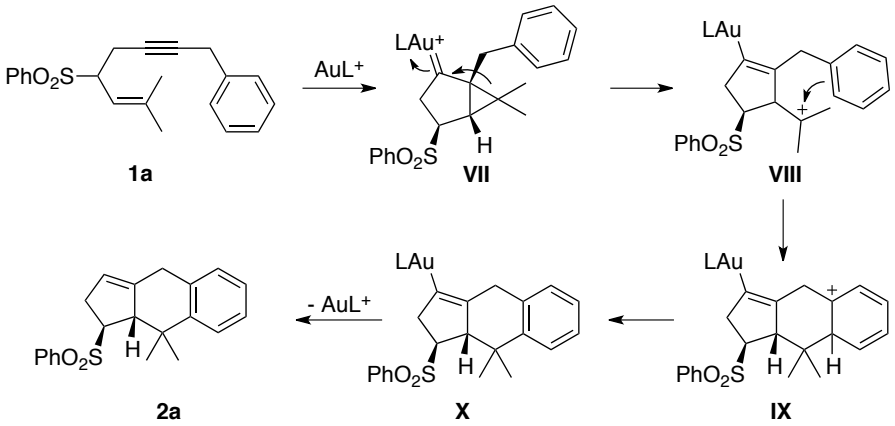
As is presented in ***Table 1***, tricyclic compounds **2** were obtained as single stereoisomers in the presence of different catalysts. In general, good yields were obtained with electrophilic catalysts **H** or **T**, although cationic catalyst **T** was the most active one (***Table 1***, entries 5 and 10). Enyne **2e**, substituted at the *meta* position of the aryl ring, led to a mixture of regioisomeric compounds **2e** and **2e'** (***Table 1***, entries 13 and 14). When the reaction was carried out in the presence of platinum complexes, lower yields were obtained requiring longer reaction times (***Table 1***, entries 6 and 7).

The cycloaddition reaction of 1,5-benzylenynes tolerates a variety of electron-donating groups. However, with enynes bearing electron-withdrawing groups in the benzyl moiety, no evidence of the tricyclic product was observed. Instead, only 1,4-dienes were isolated in low yields, in accordance with the mechanism proposed in *Chapter 1, Scheme 13*.



Scheme 13. Cycloisomerization of 1,5-benzylenyes bearing EWG.

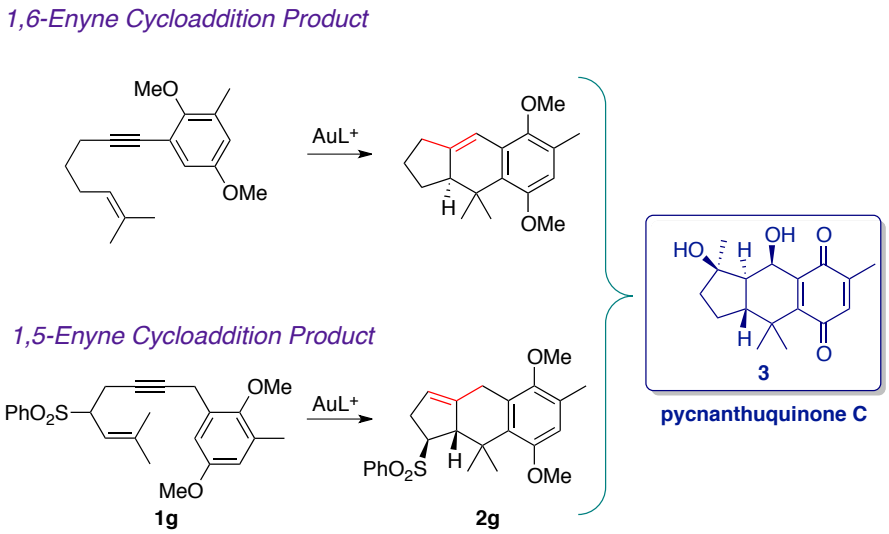
The proposed mechanism for the cycloaddition reaction of 1,5-enynes is related to that occurring in the gold(I)-catalyzed formal [4+2] cycloaddition of 1,6-arylenyne.[3] Opening of the initial cyclopropyl gold(I) carbene **VII**, followed by Friedel-Crafts alkylation gives intermediate **IX**, which by proto-demetalation leads to tricycle product **1a** (*Scheme 14*).



Scheme 14. Mechanism for the gold-catalyzed cycloaddition of 1,5-benzylenynes.

2.3.2. Application of the cycloaddition reaction toward the synthesis of pycnanthuquinone C

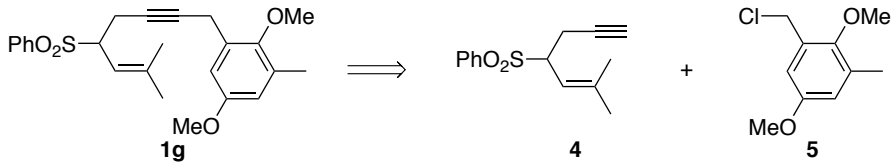
[4+2] Cycloaddition reaction of 1,6-arylenynes catalyzed by gold(I) complexes was applied for the synthesis of pycnanthuquinone C. However, functionalization of the tricyclic precursor to afford the final compound was not achieved. Therefore, the new cycloaddition reaction of 1,5-benzylenynes was applied as the key step toward the synthesis of this novel natural product **3**.



Scheme 15. Comparation between 1,5- and 1,6-cycloaddition reaction products.

The main difference between the intermediates obtained from 1,5- and 1,6-cycloaddition reaction is the position of the double bond. In the case of 1,6-enyne, the double bond is conjugated with the aromatic moiety making a more stable system. However, the double bond present in precursor **2g** is not conjugated.

Therefore, we decided to prepare **1g** by palladium cross-coupling of 1,5-enyne **4**[20] and benzyl chloride **5** (*Scheme 16*).



Scheme 16. Retrosynthesis to form 1,5-benzylenyne **1g**.

Synthesis of benzyl halide **5** starts from commercial available *o*-cresol. Bromination of **6** led to **7** in 99% yield.[21] Oxidation of **7** with CrO_3 gave 1,4-benzoquinone **8** (95% yield),[22] which was reduced with $Na_2S_2O_4$ and methylated with Me_2SO_4 to give intermediate dimethylether **10**. Formylation reaction transformed **10** in to benzaldehyde **11** in 86% yield. Benzylic alcohol **12** was obtained in 80% yield by reduction of the aldehyde with $NaBH_4$.[23] Treatment of **12** with thionyl chloride and triethyl amine yielded benzylic chloride **5** as a yellow oil in 88% yield.[24]

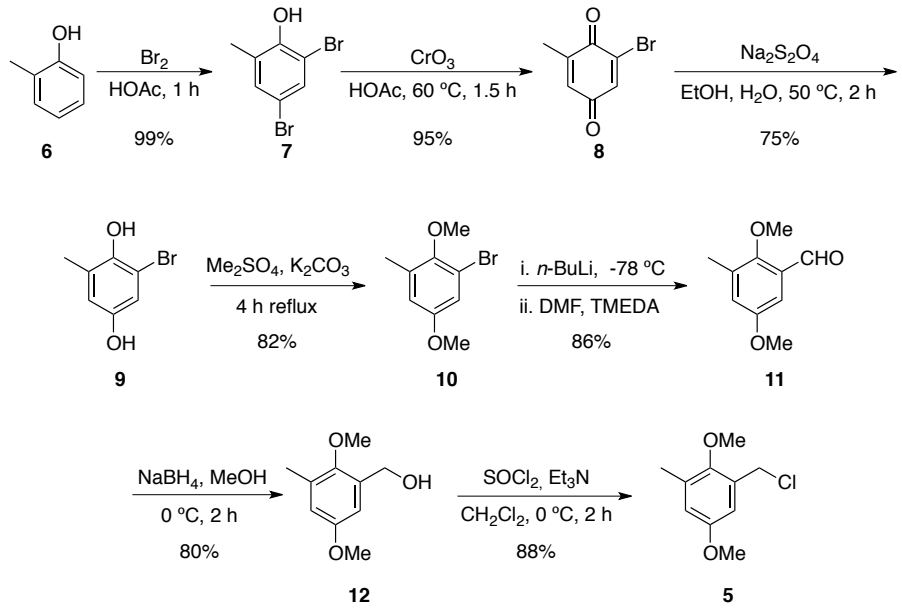
20 For the synthesis of 1,5-enynes **1**: Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721-7730.

21 Zhao, H.; Biehl, E. *J. Nat. Prod.,* **1995**, *58*, 1970-1974.

22 Maloney, D. J.; Hecht, S. M. *Org. Lett.* **2005**, *7*, 4297-4300.

23 Kostikov, A. P.; Popik, V. V. *J. Org. Chem.* **2007**, *72*, 9190-9194.

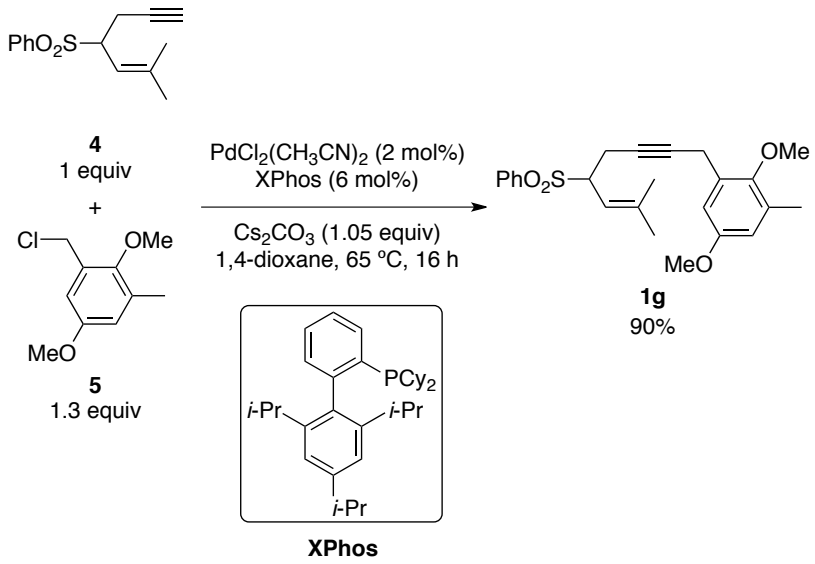
24 Giraud, A.; Vanelle, P.; Giraud, L. *Tetrahedron Lett.* **1999***, 40*, 4321-4322.



Scheme 17. Synthesis of the benzylic chloride **5**.

Benzylic-substituted 1,5-enyne **1g** was prepared by palladium-catalyzed copper-free Sonogashira coupling of the terminal alkyne of enyne **4** and the benzyl halide **5** (*Scheme 18*).[25] The catalytic system based on $PdCl_2(CH_3CN)_2$/XPhos provided excellent reactivity in the Heck alkynylation of benzyl chlorides and terminal alkynes leading 1,5-benzylenyne **1g** in 90% yield.

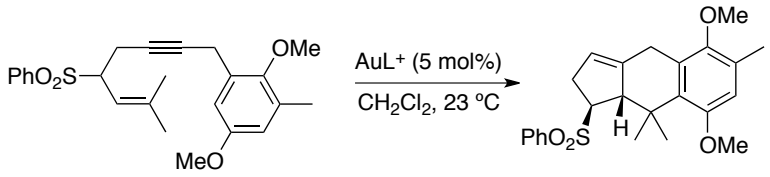
25 Pd-catalyzed benzylation (Sonogashira type) of 1,5-enynes: Larsen, C. H.; Anderson, K. W.; Andel, R. E.; Buchwald, S. L. *Synlett* **2006**, 2941-2946.



Scheme 18. Palladium-catalyzed coupling of **4** with **5**.

Cyclization of enyne **1g** was studied in the presence of two highly electrophilic gold(I) complexes under mild conditions. Most electrophilic catalyst **T** gave the tricyclic product **2g** as a single stereoisomer immediately but, due to its high reactivity caused partial decomposition of the product (67% yield) (*Table 2*, entry 1). Fortunately, less electrophilic complex **H** gave product **2g** in almost quantitative yield after 3 hours (*Table 2*, entry 2). This reaction was performed reproducibly in up to 2.5 g scale under these conditions.

Table 2. Gold(I)-catalyzed cycloaddition reaction of **1h**.



1g **2g**

entry	AuL^+	time	yield (%)
1	**T**	1 min	67
2	**H**	3 h	95

The structure and relative configuration of precursor **2g** was confirmed by X-ray diffraction (*Figure 4*).

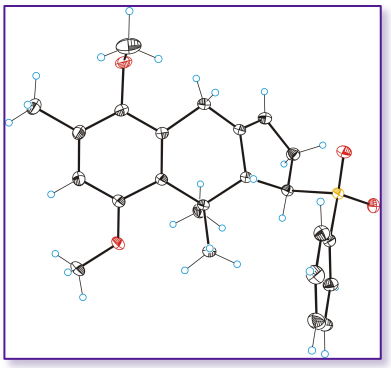
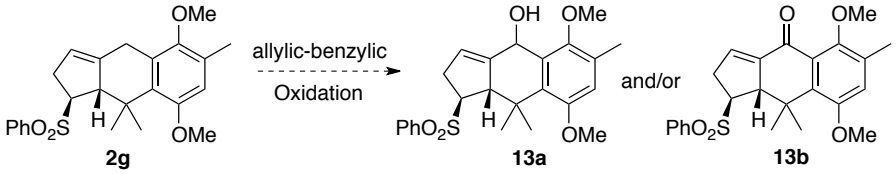


Figure 4. X-Ray structure of **2g**.

Having in mind the precedent results in the approach of 1,6-enynes toward the synthesis of this natural product, different experiments were proposed in order to functionalize **2g**. First, allylic-benzylic oxidation under a variety of conditions was assayed (*Table 3*). Unfortunately, the following reactions failed to give the desired compounds.

Attempted allylic/benzylic oxidation in the presence of dirhodium(II) caprolactamate[26] (*Table 3*, entries 1, 2 and 3) , selenium oxide[27] or Mn(III) acetate[28] using *tert*-butylhydroperoxide as a cooxidant (*Table 3*, entries 4 and 6 respectively) or pyridinium chlorochromate (PCC)[29] (*Table 3*, entry 16), gave decomposition of **2g**. Treatment with oxone (*Table 3*, entry 7), DDQ/$NaHCO_3$ (*Table 3*, entry 11), chromium trioxide[30] (*Table 3*, entry 17 and 18) or OsO_4 (*Table 3*, entry 19) led only to the recovered starting material.

Table 3. Allylic-benzylic oxidation of **2h**.



entry	reagent (equiv)	conditions	product (Yield %)
1	$[Rh_2(cap)_4]$ (0.02) *t*-BuOOH (5) $NaHCO_3$ (0.5)	CH_2Cl_2, 23 ºC	decomposition
2	$[Rh_2(cap)_4]$ (0.01) *t*-BuOOH (8)	CH_2Cl_2, 40 ºC	decomposition
3	$[Rh_2(cap)_4]$	CH_2Cl_2, 40 ºC	decomposition

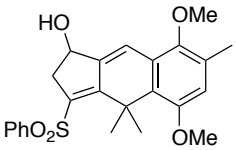
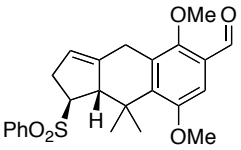
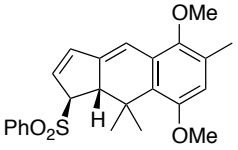
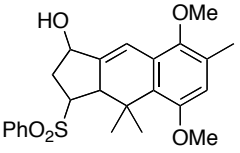
26 (a) Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622-13623. (b) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958-964.

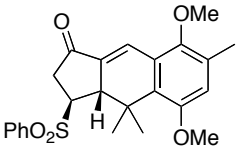
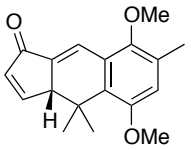
27 Carruters, W.; Coldham, I., Modern Methods of Organic Synthesis, 6.1.3, 374-377.

28 Shing, T. K. M.; Yeung; Su, P. L. *Org. Lett.* **2006**, *8*, 3149-3151.

29 Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624-633.

30 Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000-4002.

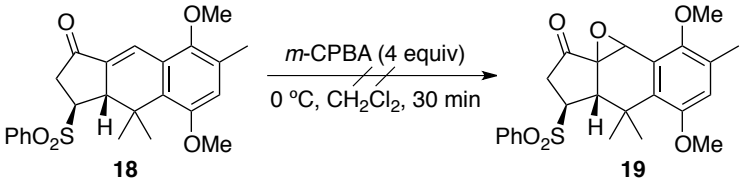
	(0.02) $NaHCO_3$ (0.5) TBHP (dec)		
4	SeO_2 *t*-BuOOH	AcOEt, 0 ºC	decomposition
5	SeO_2 (4)	CH_2Cl_2, μw 80-100 ºC	 **14** (52)
6	$Mn_3O(Ac)_9$ (0.1) *t*-BuOOH (5)	AcOEt, 23 ºC	decomposition
7	Oxone (2) $NaHCO_3$ (1)	H_2O, acetone, AcOEt	SM
8	IBX	fluorobenzene/DMSO (1:2) 85 ºC	 **15** (traces)
9	DDQ (3.3)	CH_2Cl_2 0 → 23 ºC	 **16** (60) **16** (24)
10	DDQ (3.3)	CH_2Cl_2:H_2O 0 → 23 ºC, 2 h	 **17** (43)
11	DDQ (3.3) $NaHCO_3$ (5)	CH_2Cl_2:H_2O 0 → 23 ºC, 3.5 h	SM

			16 (31) **17** (48)
12	DDQ (3.3)	CH_2Cl_2:Buffer sol.[a] 0 → 23 ºC, 3.5 h	 **18** (15)
13	DDQ (3.3)	THF:H_2O 0 → 23 ºC, 16 h	SM
14	DDQ (3.3)	dioxane:H_2O 0 → 23 ºC, 16 h	**16**
			16 (30) **17** (47)
15	DDQ (3.3) MnO_2 (3.3)	CH_2Cl_2:H_2O 40 ºC, 2 h	 **18'** (20)
16	PCC (30) NaOAc (30)	benzene, reflux, 1 h	decomposition
17	$CrO_3 \cdot pyr_2$ (2.5)	CH_2Cl_2 23 ºC, 5 h	SM
18	CrO_3·Lutidine (2.5)	isopropanol 23 ºC, 5 h	SM
19	OsO_4 (cat), NMO	23 ºC	SM

[a] Buffer solution: KH_2PO_4/K_2HPO_4 pH = 7.

When the oxidation was attempted with 2-iodoxybenzoic acid (IBX) the methyl group of the aromatic moiety was oxidized to an aldehyde in very low yield (*Table 3*, entry 8). A mixture of different oxidations products was observed when using DDQ under different conditions. Thus, diene **16** was obtained as a result of the oxidation followed by elimination of the hydroxyl group (*Table 3*, entries 9 and 14). Products **17** and **18**, resulting form oxidation with allylic isomerization, were observed when the oxidation with DDQ was carried out in a mixture of CH_2Cl_2:H_2O (*Table 3*, entries 10 and 12). Compound **18'** (*Table 3*, entry 15) presumably results by oxidation followed by elimination of the sulfone during purification by column chromatograph on silica gel.

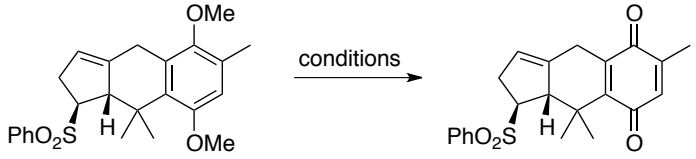
Further experiments were carried out to continue with the synthesis with ketone **18**. However, epoxidation in the presence of *m*-chloroperbenzoic acid (*m*-CPBA) or with vanadyl acetylacetonate did not lead to the desired product and decomposition was observed.



Scheme 19. Epoxidation of **18**.

Oxidation of the aromatic system to the corresponding quinone **20** was achieved successfully in moderate yield in the presence of silver oxide.[31]

Table 4. Results of the oxidation of **2g** to the quinone system.



2g **20**

entry	reagent	conditions	yield
1[32]	AgO, HNO_3 6M, dioxane	60 min, 23 ºC	50%
2[33]	$Ce(NH_4)_2(NO_3)_8$, MeCN	30 min, 23 ºC	**20** + unidentified product

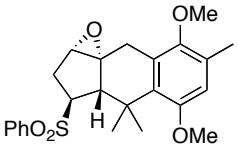
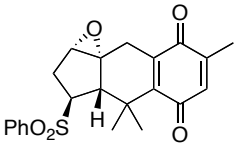
Epoxidation of **2g** with *m*-CPBA in order to obtain the oxirane **21** was carried out, as well as with substrate **20** obtaining in both cases the desired product (*Table 5*). While longer reaction times gave complete decomposition of substrate **2g** (*Table 5*, entry 1), reducing reaction time to 5 hours led to the desired epoxide in 25% and recovering 40% of the starting material (*Table 5*, entry 2).

31 Love, B. E.; Bonner-Stewart, J.; Forrest, L. A. *Synlett* **2009**, 813-817.

32 Harrowven, D. C.; Tyte, M. J. *Tetrahedron Lett.* **2001**, *42*, 8709-8711.

33 Davies, H. M. L.; Dai, X. *Tetrahedron* **2006**, *62*, 10477-10484.

Table 5. Epoxidation of **2g** and **20**.

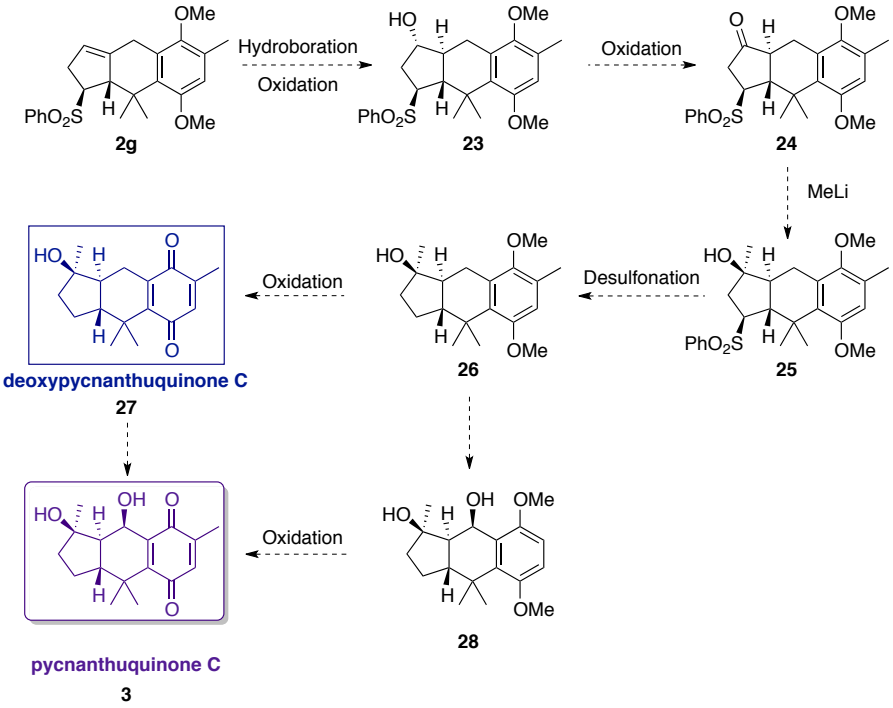
entry	substrate	reagent	conditions	product (yield %)
1	**2g**	*m*-CPBA	0 ºC, CH_2Cl_2, 16 h	decomposition
2	**2g**	*m*-CPBA	0 ºC, CH_2Cl_2, 5 h	 **21** (25)[a]
3	**20**	*m*-CPBA	0 ºC, CH_2Cl_2, 1 h	 **22** (28)

[a] 40% starting material recovered.

Three main strategies were developed in order to functionalize **2g**.

a) *Strategy 1*

This strategy consists in a 6 steps pathway to obtain **3** (*Scheme 20*). Hydroboration followed by oxidations would lead **23**, which by oxidation to the ketone and desulfonation would give **26**. At his point, two different routes to achieve pycnanthuquinone C are possible: through deoxypynanthuquinone C or, through intermediate **28**.

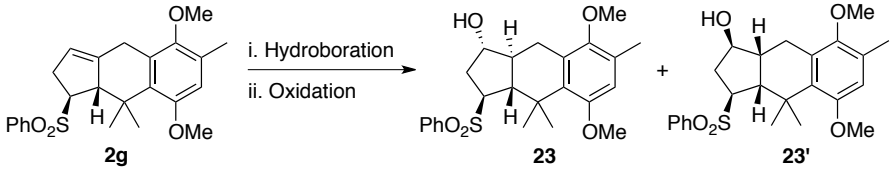


Scheme 20. Strategy 1: Synthetic pathway.

Hydroboration[34] of tricyclic precursor **2g** was carried out in the presence of different boranes. The reaction only provided the desired product in the presence of BH_3 (*Table 6*, entry 1 and 5), giving a mixture of diastereoisomers in 1:1 ratio. An excess of borane (3.5 equiv) were needed to obtain 95% yield (*Table 6*, entry 5).

34 Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1988**, *29*, 3201-3204.

Table 6. Hydroboration results of **2g**.

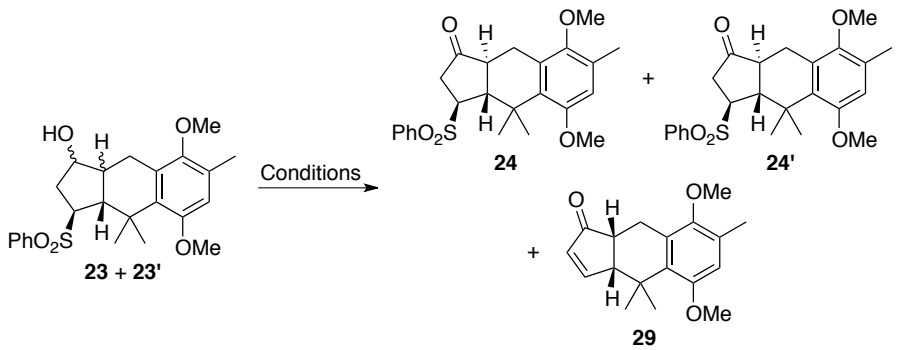


2g **23** **23'**

entry	conditions	yield (%)
1	i. BH_3·THF (1 equiv) THF, 0 ºC ii. NaOH, H_2O_2	31 1:1
2	i. 9-BBN·THF (1 equiv) THF, 0 ºC ii. NaOH, H_2O_2	decomposition
3	i. Catecholborane (2.5 equiv) THF, 0 ºC ii. NaOH, H_2O_2	SM
4	i. Catecholborane (5 equiv) THF, 0 ºC ii. NaOH, H_2O_2	SM
5	i. Pinacholborane (5 equiv) THF, 0 ºC ii. NaOH, H_2O_2	SM
6	i. BH_2SMe_2·THF (2.5 equiv) THF, 0 ºC ii. NaOH, H_2O_2	SM
7	1. BH_3·THF (3.5 equiv) THF, 0 ºC 2. NaOH, H_2O_2	95 1:1

Swern[35] and Dess-Martin[36] oxidation conditions were applied to the mixture of hydroboration products (*Table 7*). The best results were obtained using the DMP reagent leading to **24** in 40% yield (*Table 7*, entry 2). In both oxidations, mixtures of products **24** and **29** were observed. α,β-Unsaturated ketone **29** is formed during purification by column chromatography on silica gel facilitating the elimination of the sulfone moiety in one of the isomer derived from **23'**. When the reaction was carried out without further purification, a mixture of diastereoisomers was obtained in 98% yield (*Table 7*, entry 3).

Table 7. Results of the oxidation of **23** and **23'**.



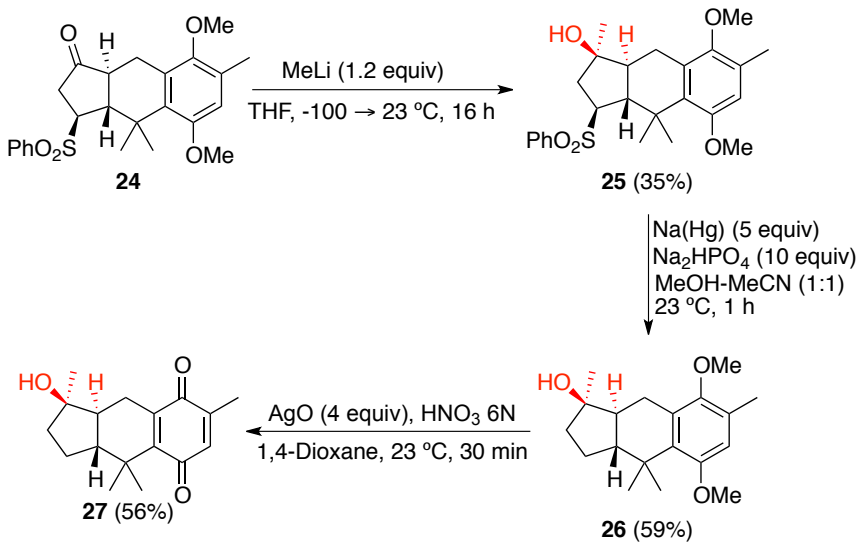
entry	conditions	product (Yield %)
1	i. Oxalyl chloride (1.2 equiv) DMSO, -78 ºC, CH_2Cl_2 ii. Et_3N	**24** (20) + **29** (8)
2	DMP (1.5 equiv), $NaHCO_3$ (5 equiv) 0 → 23 ºC, CH_2Cl_2	**24** (40) + **29** (18)
3	DMP (1.5 equiv), $NaHCO_3$ (5 equiv) 0 → 23 ºC, CH_2Cl_2	**24** + **24'** (98)[a] 1:1 ratio

[a] No purification was done.

35 Ryu, J.-S.; Marks, T. J.; McDonald, F. E. *Org. Lett.* **2001**, *3*, 3091-3094.

36 Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549-7552.

Treatment of ketone **24** with MeLi[37] gave the methylated product **25** with the relative configuration proposed for pycnanthuquinone C (*Scheme 21*). Reductive elimination of **25** with sodium amalgam[38] in the presence of protic solvent followed by oxidation of the aromatic ring with AgO[31] led to deoxypycnanthuquinone C **27** in 56% yield.



Scheme 21. Synthesis of deoxypycnanthuquinone C **32**.

The aliphatic C-H oxidation reaction of **27** in the presence of an iron-based catalyst and hydrogen peroxide failed to give the desired product.[39]

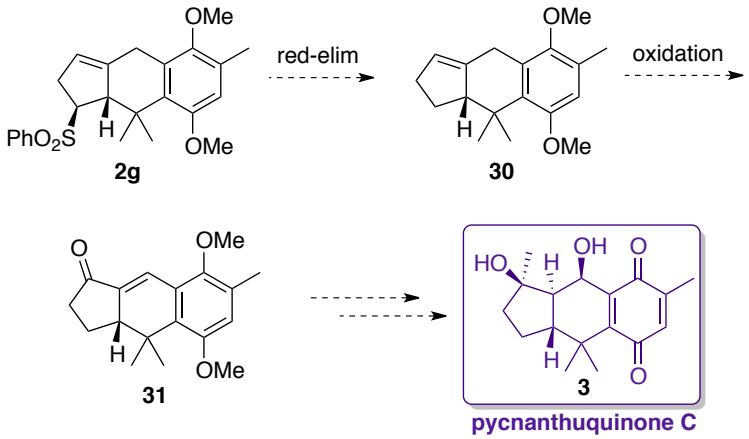
37 (a) Li, H.; Mehta, G.; Padma, S.; Le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2006-2011. (b) Groth, U.; Kesenheimer, C.; Kreye, P. *Synlett* **2006**, 2223-2226. (c) Enders, D.; Leriverend, C. *Tetrahedron: Asymmetry* **1997**, *8*, 2787-2792.

38 (a) Méndez, M. *Doctoral Thesis*, UAM, **2001**. (b) Jolivet, B.; Uguen, D. *Tetrahedron Lett.*, **2002**, *43*, 7907.

39 Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783-787.

b) *Strategy 2*

We also considered the removal of the sulfone in the first step (*Scheme 22*).

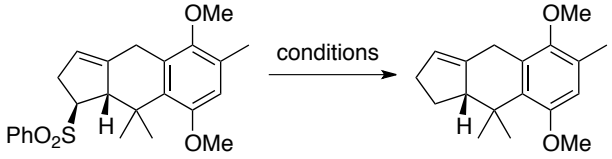


Scheme 22. Alternative strategy toward the synthesis of **3**.

Firstly, a study to optimize the reductive elimination was done.[38,40] Amalgams with Group IA-IIIA metals in alcoholic solvents have been recommended for this reaction. The most significant results of these assays are shown in *Table 8*.

40 Examples of reductive-elimination. Sm-based: (a) Knowles, H.; Parsons, A. F.; Pettifer, R. M. *Synlett* **1997**, 271-272. (b) Muñoz, L.; Rosa, E.; Bosch, M. P.; Guerrero, A. *Tetrahedron Lett.* **2005**, *46*, 3311-3313. (c) Keck, G. E.; Savin, K. A.; Weglarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194-3204. Na-based: (d) Yang, H.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2008**, *130*, 9238-9239. Li-based: (e) Coltart, D. M.; Danishefsky, S. J. *Org. Lett.* **2003**, *5*, 1289-1292.

Table 8. Studies on the reductive-elimination in **2g**.



2g **30**

entry	reagent	conditions	yield% (SM %)
1	Na(Hg) (2 equiv) Na_2HPO_4(2.4 equiv)	23 ºC MeOH:MeCN	16
2	Na(Hg) (4 equiv) Na_2HPO_4 (5 equiv)	23 ºC MeOH:MeCN	16 (40)
3	Na(Hg) (10 equiv) Na_2HPO_4 (12 equiv)	23 ºC MeOH:MeCN	85
4	Na(Hg) (10 equiv) Na_2HPO_4(12 equiv)	23 ºC MeOH:MeCN	22
5	SmI_2 (3 equiv)	0 → 23 ºC	0 (<99)
7	SmI_2 (5 equiv)	-20 → 23 ºC	0 (<99)
8	$Li^+(C_{10}H_8)^-$	23 ºC THF	decomposition
9	Mg (30 equiv)	-20 → 23 ºC MeOH	n.d. (50)
10	Mg (30 equiv)	50 → 65 ºC MeOH	28 (72)
11	Mg powder (30 equiv)	0 → 23 ºC MeOH	5 (38)
12	Mg powder act (30 equiv)	50 ºC MeOH	0 (<99)
13	Mg powder act (30 equiv)	50 ºC MeOH	0 (<99)

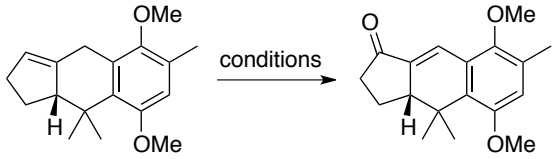
n.d.: not determined

Desulfurization using Na/Hg amalgam in the presence of phosphate gave the best results providing **30** in excellent yield (*Table 8*, entry 3). In contrast, SmI_2, Mg or lithium naphthalenide were not found to be reliable desulfonylation reagents in our case.

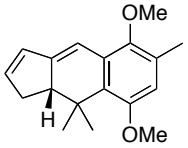
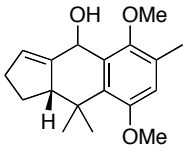
Oxidation of **30** in the presence of dirhodium(II) caprolactamate using *tert*-butylhydroperoxide as a co-oxidant or OsO_4 together with *N*-methylmorpholine-*N*-oxide (NMO) as co-oxidant failed, recovering only the starting material (*Table 9*, entry 5 and 6). It is worth to mention that when DDQ or selenium oxide[41] were used, oxidized product **33** was obtained (*Table 9*, entry 2 and 4). However, due to its instability further optimization was unsuccessful. The desired product **31** was obtained when chromium trioxide-3,5-dimethyl pyrazol complex was used as the oxidizing agent (*Table 9*, entry 3). However, this reaction provided highly variable yields (10-90%) and could not be reproduced easily.

41 Zhou, Q; Chen, X.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 3513-3516.

Table 9. Allylic-benzylic oxidation of **31**.

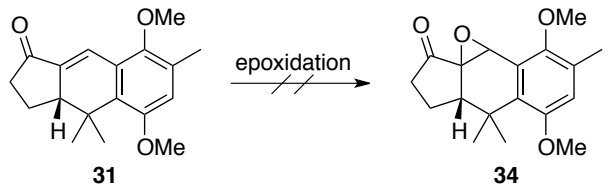


30 **31**

entry	reagent	conditions	product (yield %)
1	DDQ (3.3 equiv)	0 → 23 ºC CH_2Cl_2:H_2O	 **32** (35)
2	DDQ	23 ºC CH_2Cl_2: Buffer sol.[c]	 **33** (12)[a]
3	CrO_3-DMP (2.7 equiv)	23 ºC CH_2Cl_2	**31** (10-90)[b]
4	SeO_2 /*t*-BuOOH Salicylic acid	23 ºC CH_2Cl_2	**33** (44)
5	$[Rh_2(cap)_4]$ *t*-BuOOH, $NaHCO_3$	40 ºC CH_2Cl_2	SM
6	OsO_4, NMO	23 ºC THF:Acetone:buffer[c]	SM

[a] Unstable product. [b] Oxidation with CrO_3 was not reproducible. [c] Buffer solution: KH_2PO_4/K_2HPO_4 pH = 7.

We try to continue with the synthesis of pycnanthuquinone C from **31**. Epoxidation of the double bond was assayed under several conditions (*Scheme 23*). No reaction was observed with *m*-chloroperbenzoic acid (*m*-CPBA), tetrabutylammonium peroxydisulfate [42] /H_2O_2, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) with TBHP as co-oxidant,[43]or basic conditions as NaOH/TBHP.[44] The use of vanadyl acetylacetonate system also failed to give the desired keto-epoxide leading to decomposition products.



31 **34**

Scheme 23. Epoxidation of **31**.

Different procedures were applied in order to functionalize the double bond in **31**. Copper-catalyzed β-boration of α,β-unsaturated carbonyl compounds in the presence of bis(pinacolato)diboron and DPE-phos as ligand was reported to give the corresponding β-boryl carbonyl compounds in high yield.[45] However, this procedure failed with substrate **31**. When (*R*,*R*)-QuinoxP* was used as ligand or the reaction was carried out in the presence of $NaBO_3 \cdot 4H_2O$, no product of β-borylation was observed neither.[46]

42 Yang, S. G.; Hwang, J. P.; Park, M. Y.; Lee, K.; Kim, Y. H. *Tetrahedron* **2007**, *63*, 5184-5188.

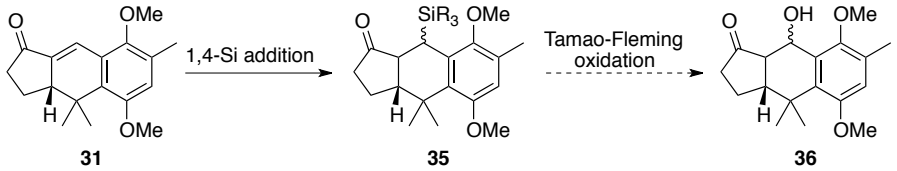
43 Nicolaou, K. C.; Lim, Y. H.; Becker, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 3444-3448.

44 Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, *120*, 8661-8673.

45 Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887-4889.

46 For enantioselective conjugated borylation see: (a) Chen, I. H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664-11665. (b) Schiffner, J. A.;

Furthermore, conjugated addition of silyl groups to *β*-unsaturated enones and its posterior oxidation from Si to OH conversion[47] to give **36** was attempted by addition of phenyldimethylsilyl cuprate reagent at -78 ºC without any success (*Scheme 24*).[48,49]



31 **35** **36**

Scheme 24. Conjugated addition of silyl groups to **31**.

Grignard addition of MeMgBr to the carbonyl moiety in **31** was carried out successfully in the presence of THF-soluble lanthanide salt ($LaCl_3 \cdot 2LiCl$) (*Scheme 25*).[50] A mixture of alcohols was obtained in 46% yield. Unfortunately, it was not possible to carry out further experiments with **37** or **37'** due to their ready decomposition.

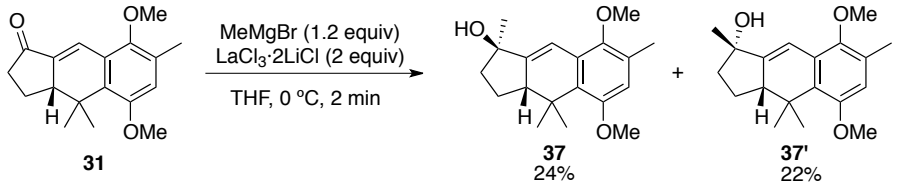
Müther, K.; Oestreich, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1194-1196. (c) Lee, K.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253-7255.

47 For Tamao-Fleming oxidation references see: (a) Bracegirdle, S.; Anderson, E. A. *Chem. Comm.* **2010**, *46*, 3454-3456. (b) Reddy, P. V.; Koos, P.; Veyron, A. l.; Greene, A. E.; Delair, P. *Synlett* **2009**, 1141-1143. (c) Schmidt, A. W.; Olpp, T.; Schmid, S.; Goutal, S.; Jäger, A.; Knölker, H.-J. *Synlett* **2007**, 1549-1552.

48 Fleming, I.; Maiti, P.; Ramarao, C. *Org. Biomol. Chem.* **2003**, *1*, 3989-4004.

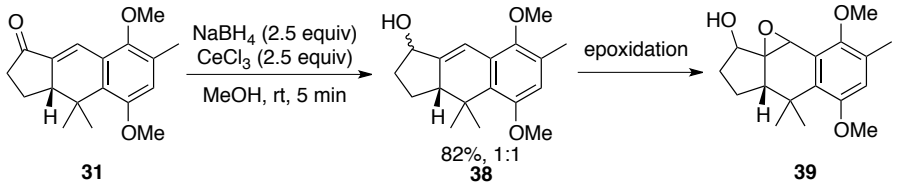
49 For 1,4-conjugated addition of silyl groups see: (a) Fleming, I.; Lee, D. *Tetrahedron Lett.* **1996**, *37*, 6929-6930. (b) Kokesh, F. C.; Hine, J. *J. Org. Chem.* **1976**, *41*, 1976-1979. (c) Blay, G.; Collado, A. M.; García, B.; Pedro, J. R. *Tetrahedron* **2005**, *61*, 10853-10860. (d) Tang, Z.; Mathieu, B.; Tinant, B.; Dive, G.; Ghosez, L. *Tetrahedron* **2007**, *63*, 8449-8462. (e) Lee, K-S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898-2900.

50 Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497-500.

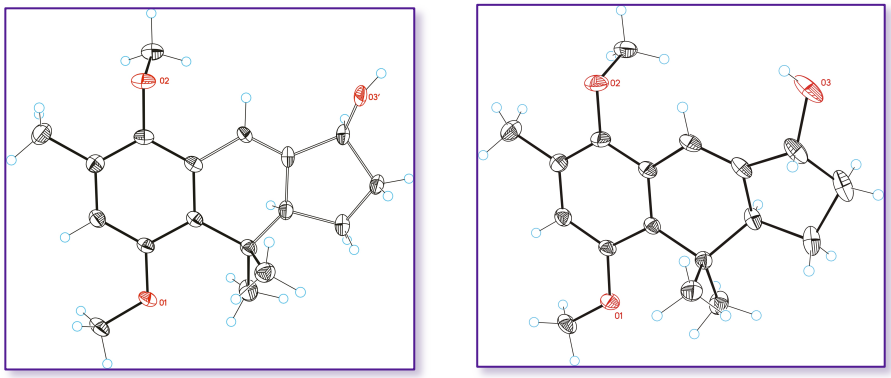


Scheme 25. Addition of MeMgBr to **31**.

In parallel, reduction of ketone **31** was performed in the presence of $NaBH_4/CeCl_3$ in good yield obtaining a 1:1 diastereomeric mixture of alcohols **38** (*Scheme 26*). The structure of product **38** and its diastereoisomer **38'** was confirmed by X-ray difraction (*Figure 5*). Unfortunately, epoxidation of **38** in the presence of $VO(acac)_2$ and TBHP as co-oxidant gave a complex mixture impossible to characterize. Other epoxidation methodes led to decomposition.



Scheme 26. Alternative assays toward the synthesis of pycnanthuquinone C.

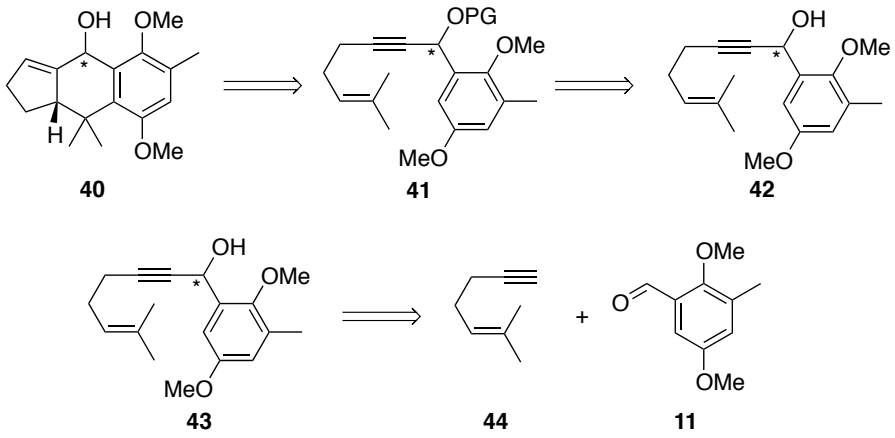


38 **38'**

Figure 5. X-Ray structure of **38** and **38'**.

c) *Strategy 3*

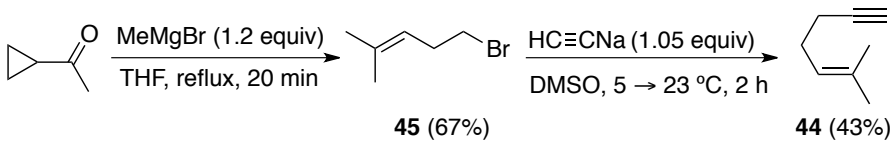
We tried to obtain pycnathuquinone C through an enantioselective pathway (*Scheme 27*). This strategy involves the preparation of 1,5-enyne **44** without the sulfone moiety and its addition of the corresponding benzaldehyde **11** following the enantioselective protocol developed by Carreira's research group.[51]



Scheme 27. Strategy 3: Enantioselective synthesis of pycnanthuquinone C.

51 Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605-2606.

Synthesis of 1,5-enyne **40** involves the preparation of 5-bromo-2-methyl-2-pentene **45** following a know method.[52] Enyne **44** was obtained by distillation as colorless oil in 43% yield (*Scheme 28*).[53] Unfortunately, all attempts to obtain **42** applying the methodology developed by Carreira failed.



Scheme 28. Synthesis of 1,5-enyne **44**.

At this point, we decided to go back and try to develop a new enantioselective route starting from the cycloaddition reaction of 1,6-arylenynes (*Strategy 4*).

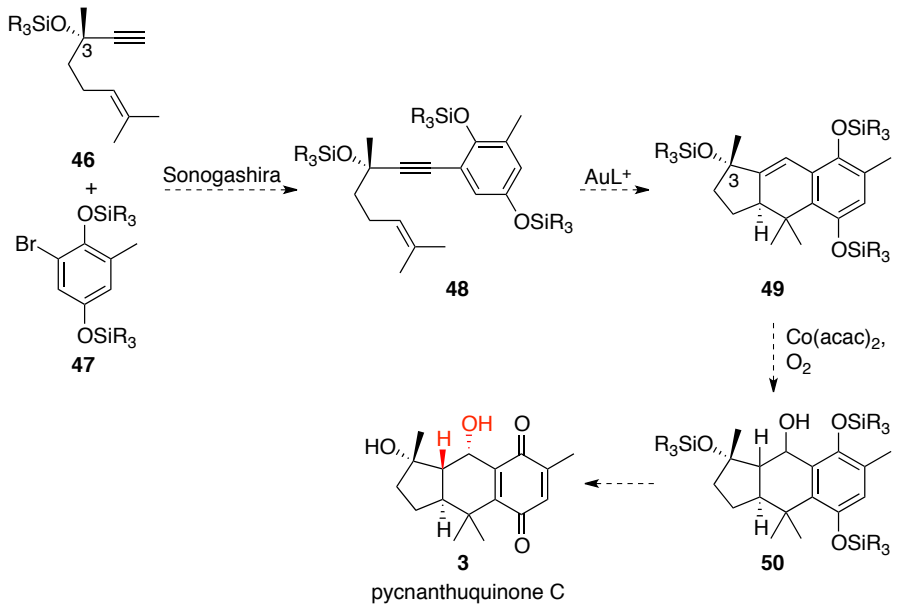
d) *Strategy 4*[54]

In the new pathway we proposed a Sonogashira cross-coupling reaction of enantiomerically pure enyne **46** and aryl bromide **47** to obtain **48** (*Scheme 29*). Gold catalyzed cyclization reaction of **48** will lead to tricyclic precursor **49** which could be further oxidized to adduct **50** in a cobalt(II) catalyzed oxidation reaction. Deprotection of the silyl groups under oxidative conditions would lead to intermediate **3**.

52 Biernacki, W.; Gdula, A. *Synthesis* **1979**, 37–38.

53 (a) Fish, P. V. *Synth. Commun.* **1996**, *26*, 433-444. (b) Jacobi, P. A.; Kaczmarek, C. S. R.; Udodong, U. E. *Tetrahedron* **1987**, *43*, 5475-5488.

54 Work developed in collaboration with Dr. Paul McGonigal at ICIQ.



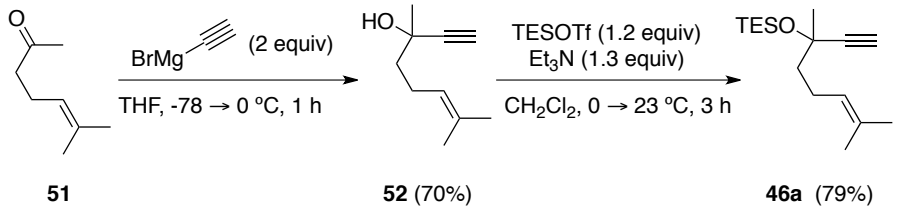
Scheme 29. Proposed 1,6-enyne pathway toward the sysnthesis of **3**.

Enyne **46** has the required functional groups as the final natural product at position 3. As mentioned in the introduction of this chapter, 1,6-arylenynes containing a hydroxyl group at position 3 or a protected hydroxyl with MOM, methyl, TEM, PMB, *t*-butyl acetate or CO_2CF_3, failed to give any tricyclic product in the presence of gold catalysts. In this cases, one of the challenges of the cyclization of enyne **48** was to avoid the migration of the hydroxyl group.[55]

First of all, we carried out the synthesis of the racemic 1,6-enyne as shown below in *Scheme 30*. Enyne **52** was obtained in 70% yield following a known procedure.[56] Protection with TES group gave enyne **46a** in excellent yield.

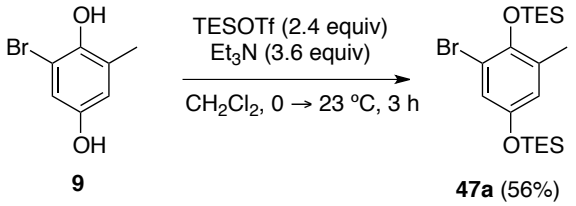
55 Migration of hydroxyl-groups in the cyclization of enynes: Jiménez-Núñez, E.; Raducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6152-6155.

56 Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2002**, *124*, 5025-5036.



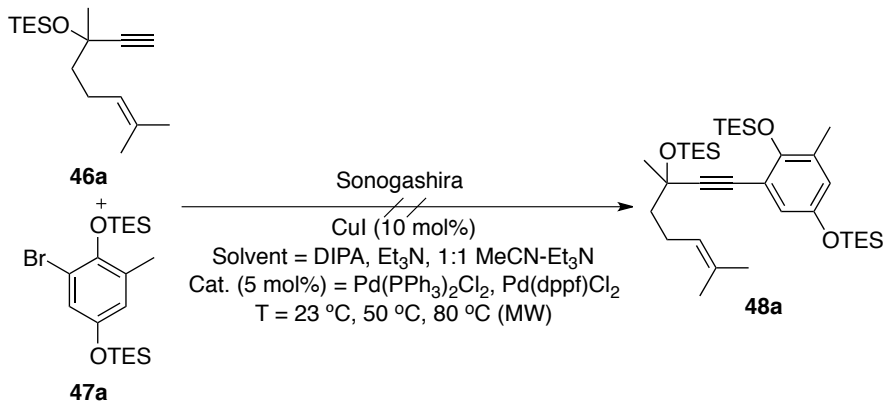
Scheme 30. Synthesis of enyne **46a**.

Aryl bromide **47a** was prepared from diphenol **9** (for preparation of 9 see *Scheme 17*) by protection with triethylsilyltriflate in 79% yield (*Scheme 31*).



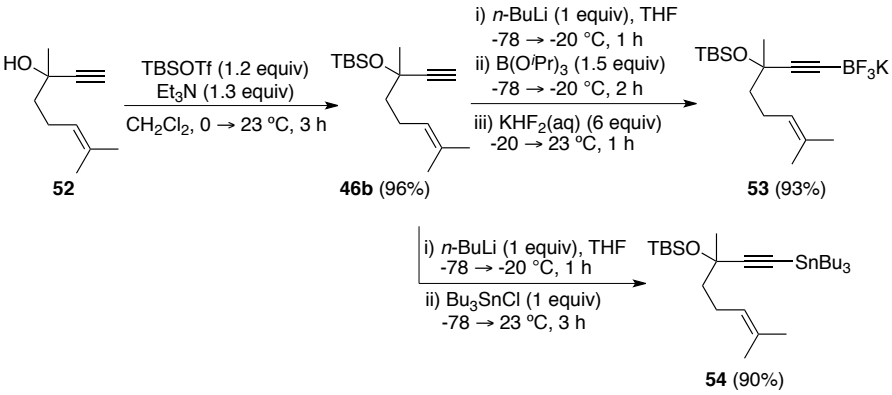
Scheme 31. Synthesis of arylbromide **47a**.

Alkynyl-aryl coupling of **47a** and **46a** was attempted by a Sonogashira reaction in the presence of $Pd(PPh_3)_2Cl_2$ or $Pd(dppf)Cl_2$ as catalysts under different conditions. However, no conversion or deprotection of the TES group was observed (*Scheme 32*). Therefore, other methods such as Suzuki or Stille cross-coupling reactions were tried for the synthesis of the desired enyne.



Scheme 32. Sonogashira conditions for the synthesis of **48a**.

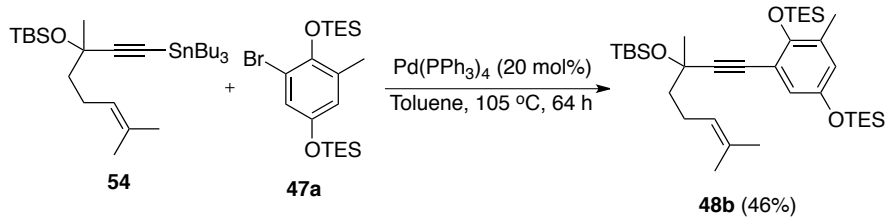
Preparation of enynes **53** and **54** required the protection of the hydroxyl group present in **52** with *t*-butyldimethylsilyltriflate to avoid the deprotection of the TES group of **48a** in the presence of *n*-BuLi. Enynes **53** and **54** were prepared by deprotonation of the alkyne followed by the formation of the Molander salt or by the formation of the stannane respectively.



Scheme 33. Preparation of enynes **53** and **54**.

Whereas Suzuki cross-coupling reaction of **53**[57] gave deprotection of the TES group present in the arylbromide moity, the desired product **48b** was obtained by a Stille cross-coupling of **54** in 46% yield.

Stille Coupling



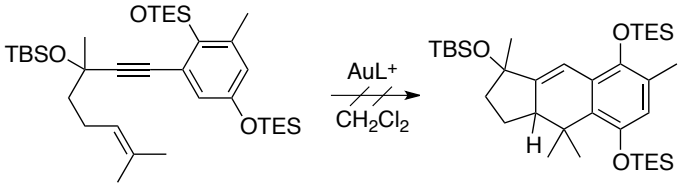
54 **47a** **48b** (46%)

Scheme 34. Stille coupling of **54**.

Therefore, cyclization studies were carried out with arylenyne **48b** in the presence of different gold complexes (*Table 10*). Unfortunately, cyclization was not successful with any gold(I) or gold(III) catalyst. Even heating to 70 ºC under microwave irradiation only resulted in recovery of starting material.

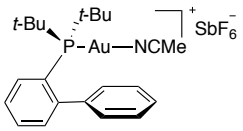
57 Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416-8423.

Table 10. Cyclization studies of **48b** in the presence of gold(I) complexes.

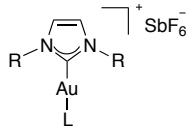


48b **49b**

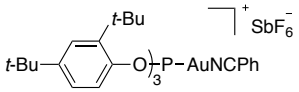
entry	AuL^+	time	temp (ºC)	yield (%)
1	**H**	15 h	23	SM
2	**H**	15 min	70	SM
3	**R**	15 h	23	SM
4	**R**	15 min	70	SM
5	**T**	15 h	23	SM
6	**T**	15 min	70	SM
7	**Y**	15 h	23	SM
8	**Y**	15 min	70	SM
9	**U**	15 min	70	SM
10	$AuCl_3$	15 min	70	SM



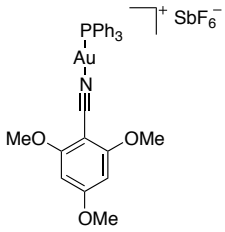
H



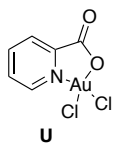
R: R = 2,6-*i*-$Pr_2C_6H_3$, L = PhCN



T

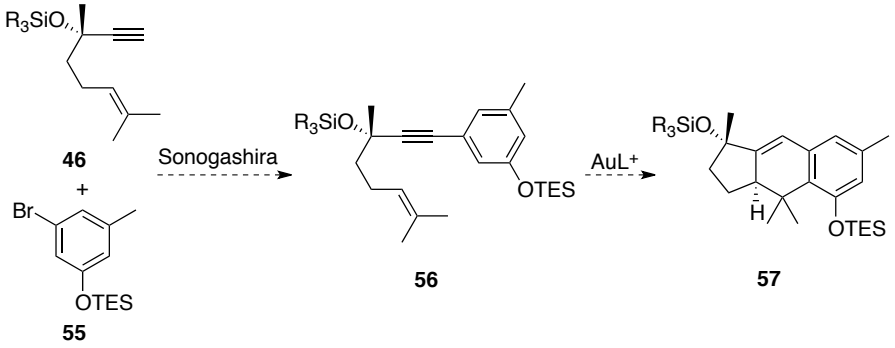


Y



U

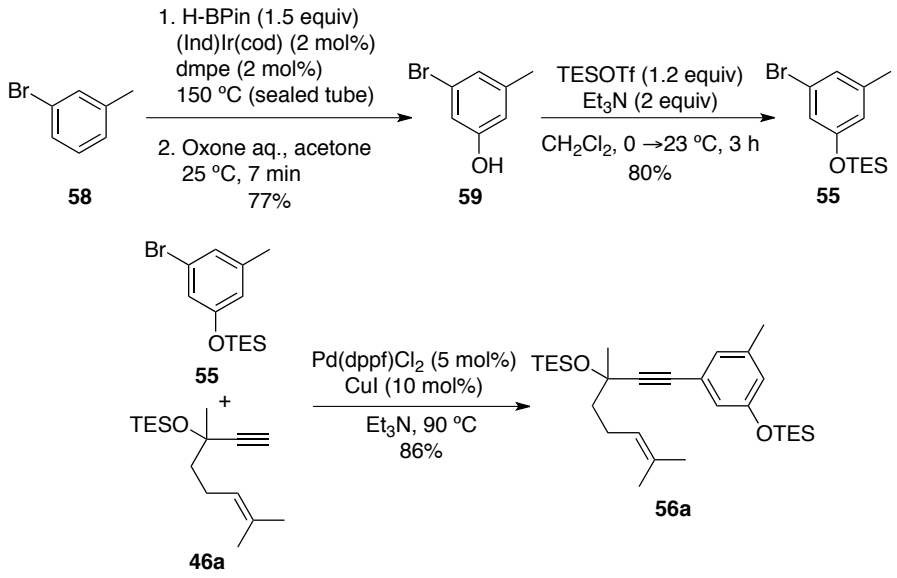
To decrease the steric hindrance, we synthesized a less substituted arylbromide **55** (*Scheme 35*).



Scheme 35. Alternative approach of 1,6-enyne route.

Aryl bromide **55** was synthesized from commercially available 3-bromotoluene (**58**) via a one-pot C-H activation-borylation-oxidation to give phenol **59** in 77% yield.[58] Protection of the phenol with triethylsilyltriflate gave the desired aryl bromide **55** in 80% yield (*Scheme 36*). Sonogashira cross-coupling between **55** and 1,6-enyne **46a** lead to 1,6-arylenyne **56a** in 86% yield.

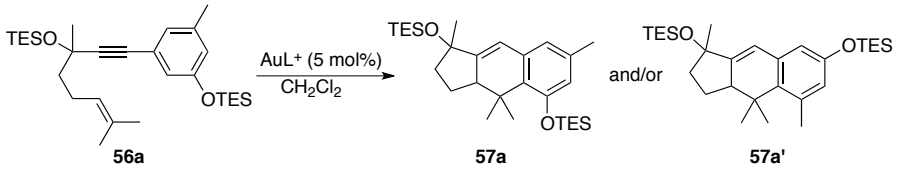
58 Norberg, A. M.; Smith III, M. R.; Maleczka Jr, R. E. *Synthesis* **2011**, 857-859.



Scheme 36. Synthesis of aryl enyne **56a**.

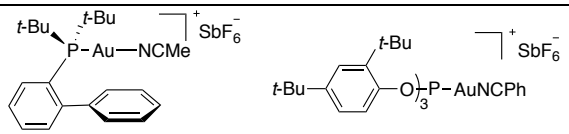
Cyclization of **56a** could lead to a mixture of products **57a** and **57a'** due to Friedel-Craft type reaction at the two *ortho* positions present on the aryl ring. Unfortunately, starting material was recovered in the cyclization **56a** in the presence of gold(I)-complexes bearing phosphine or phosphite ligands (*Table 11*, entry 1 and 2). Decomposition of the starting material was observed when heated to 60 ºC in the presence of complex **T** (*Table 11*, entry 3).

Table 11. Cyclization studies of 1,6-arylenyne **56a**.



56a **57a** **57a'**

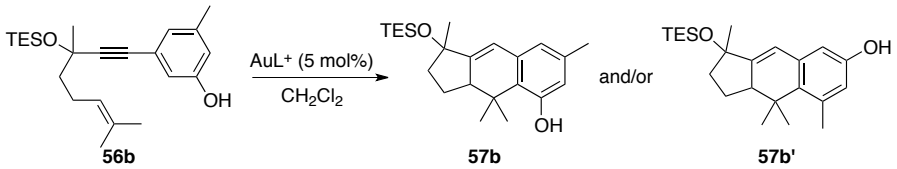
entry	AuL^+	time	temp (°C)	yield (%)
1	**H**	2 d	23	SM
2	**T**	2 d	23	SM
3	**T**	1 h	60	decomposition



H **T**

Cyclization of 1,6-arylenyne **56b** which has a free phenol in the aryl moiety was also studied.

Table 12. Cyclization studies of 1,6-arylenyne **56b**.

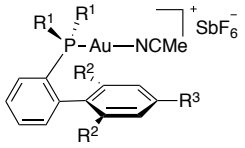


56b **57b** **57b'**

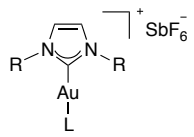
entry	AuL^+	time (h)	temp (°C)	product (yield%)
1	**H**	16	23	**57b**+**57b'** (28) ratio 1:2.4[c] **57c**+**57c'** (10) ratio 1:1.4[c]
2[a]	**H**	24	23	decomposition
3[a]	**U**	24	23	decomposition
4[a]	**R**	24	23	decomposition

5	**R**	24	23	decomposition
6[a]	**Q**	24	23	decomposition
7	**Q**	24	23	decomposition
8	**T**	16	23	decomposition
9	**T**	24	23	decomposition
10	**T**	24	-40	decomposition
11	**I**	13	23	decomposition
12	**G**	24	23	decomposition
13	$Au(PPh_3)Cl/AgSbF_6$	13	23	**57c**+**57c'** (10) ratio 1:1.4[c]

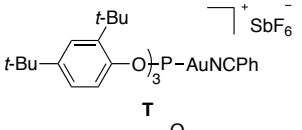
[a] Reactions were carried out in $CHCl_3$. [b] 10 mol% catalyst loading. [c] Ratio not assigned to each product



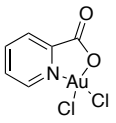
G: R^1 = Cy, R^2 = R^3 = H
H: R^1 = *t*-Bu, R^2 = R^3 = H
I: R^1 = *t*-Bu, R^2 = R^3 = *i*-Pr



Q: R = 2,4,6-$Me_3C_6H_2$
L = 2,4,6-$(MeO)_3C_6H_2CN$
R: R = 2,6-*i*-$Pr_2C_6H_3$
L = PhCN

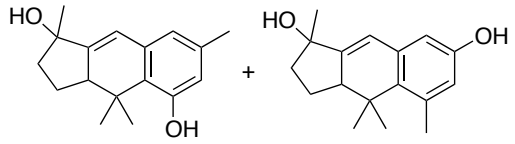


T



U

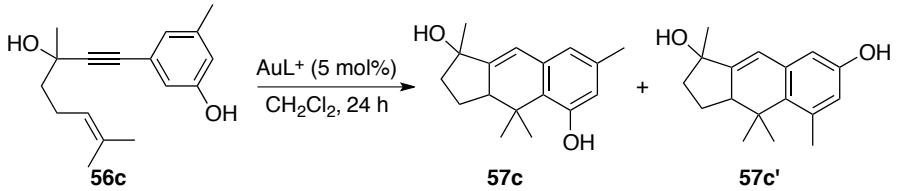
Cyclization with of complex **H** gave a mixture of the four products (*Table 12*, entry 1): products **57b** and **57b'** in low yield together with a mixture of other two compounds **57c** and **57c'** (*Figure 6*) resulting from the elimination of the TES protecting group. Unfortunately, it was not possible to separate compounds **57b** and **57b'** and we could not determine which of the tricyclic adducts is the major one. In the presence of $Au(PPh_3)Cl/AgSbF_6$ deprotection of the TES group was also observed, leading to a mixture of **57c** and **57c'** isolated in 10% yield. Furthermore, when the cyclization took place in the presence of gold complexes bearing phosphite (*Table 12*, entries 8 and 9) or NHC-carbene ligands (*Table 12*, entries 4-7), as well as gold(III) catalyst **U** (*Table 12*, entry 3) only decomposition of the starting material was observed.



57c **57c'**

Figure 6. Additional products obtained with gold catalyst **H**.

Due to the formation of complex mixtures of products observed in these reactions, an alternative approach based on the cyclization of the 1,6-arylenyne without protecting groups was studied. Reaction of **56c** with catalyst **H**, **R** or **T** led to a mixture of **57c** and **57c'** 1:1 in low yield.



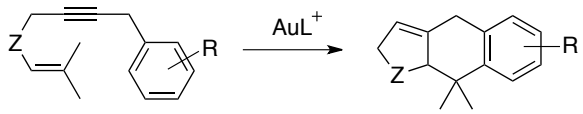
56c **57c** **57c'**

Scheme 37. Cyclization of 1,6-enyne **56c**.

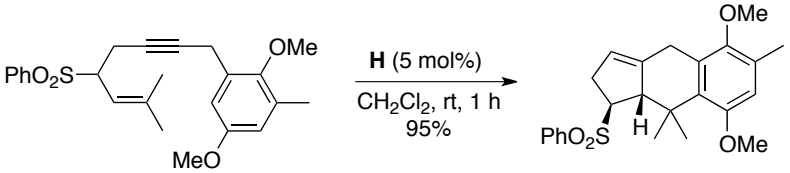
2.4. Conclusions

2.4.1. Intramolecular cycloaddition reaction of 1,5-benzylenyes

The new cycloaddition reaction of benzyl substituted 1,5-enynes takes place resulting in tricyclic products with good to excellent yields in the presence of highly electrophilic phosphite and phosphine gold(I) complexes. The reaction proceeds through cyclopropyl gold(I) carbenes of type **I**, which evolve through a Friedel-Crafts-type process in a manner related to that of 1,6-arylenynes.



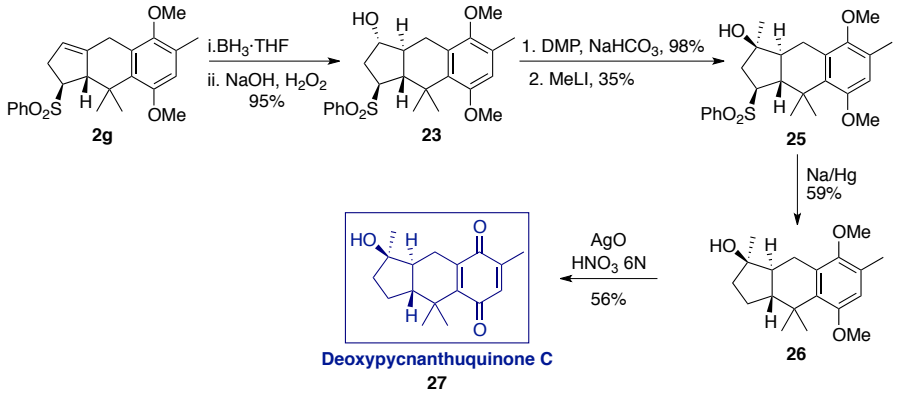
Cyclization methodology of 1,5-benzylenynes has been applied successfully as the key step toward the synthesis of pycnanthuquinone C in excellent yield by using cationic gold(I) complex **H** bearing phosphine as ligand.



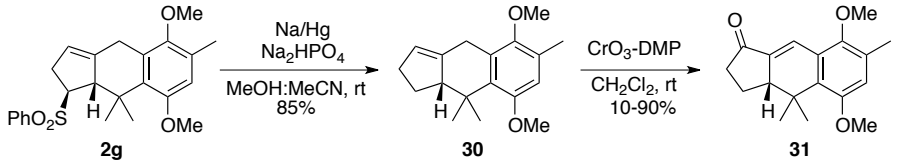
1g **2g**

2.3.2. Application of the cycloaddition reaction toward the synthesis of pycnanthuquinone C

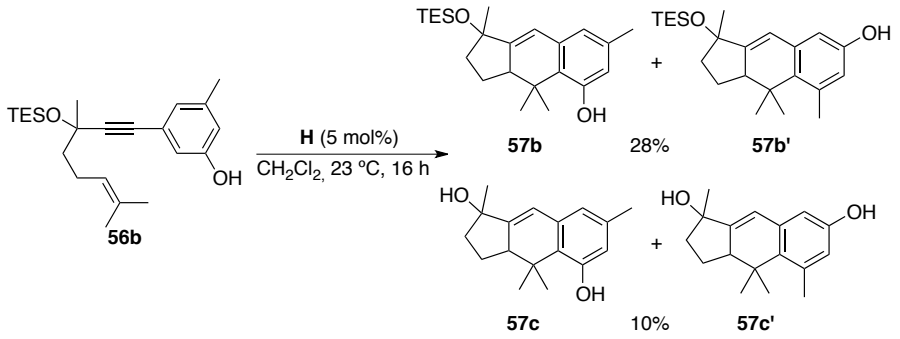
A first approach toward the total synthesis of pycnanthuquinone C led to the formation of deoxypycnanthuquinone C with the relative configuration corresponding to pycnanthuquinone C.



Other efforts to synthesize this novel natural product with different strategies led to the formation of possible precursors of pycnanthuquinone C. Strategy 2, starting with the desulfurization of **2g** led to compound **31**. However, all the attempts to obtain pycnanthuquinone C were unsuccessful.



A new approach based on the cycloaddition of 1,6-arylenynes was applied as the key step of the synthesis yielding in a mixture of four different tricyclic products.



2.5. Experimental Section

General Procedure

All reactions were carried out under Ar in solvents dried using a Solvent Purification System (SPS). Thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck GF_{234}). Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm). NMR spectra were recorded at 23 ºC on a Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatus. Mass spectra were recorded on a Waters LCT Premier (ESI) and Waters GCT (EI, CI) spectrometers. Melting points were determined using a Büchi melting point apparatus.

Complex **F**[3a] was used as received from Aldrich. The following gold(I) complexes were prepared according to described procedures: **G**,[3a] **I**,[3a] **Q**,[20] **R**,[20] **T**,[20] **W**[59] and **U**[60].

Compounds **4**,[20] **44**,[52] **45**,[52] **46a**,[55b] **46b**,[56] **52**,[56] **59**[58] were synthesized according to literature.

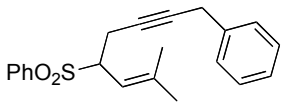
59 Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306-6316.

60 Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejović, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545-6547.

Preparation of Substrates

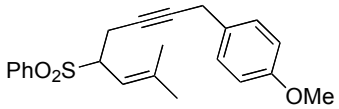
General procedure 1: synthesis of 1,5-benzylenynes. A disposable microwave tube with a stirring bar was charged with $PdCl_2(CH_3CN)_2$ (0.02 equiv), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (0.06 equiv), Cs_2CO_3 (1.05 equiv) and **4** (1.3 equiv). If the benzyl chloride was a solid it was also added at this time (1.3 equiv). The tube was evacuated and back-filled with argon three times. 1,4-Dioxane and the corresponding benzyl chloride were added and the solution (0.2 M) was heated at 65 ºC for 14 h. The reaction was monitored by GC analysis. After cooling to room temperature, the product was filtered through Celite®, and concentrated to dryness under reduced pressure. Purification by column chromatography on silica gel provided the 1,5-benzylenynes products.

(7-Methyl-5-(phenylsulfonyl)oct-6-en-2-ynyl)benzene (1a)



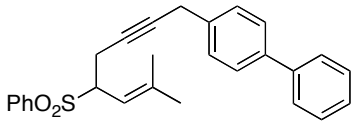
1,5-Benzylenyne **1a** was synthesized following the general procedure 1, starting from **4** (200.0 mg, 0.81 mmol) and benzyl chloride (0.094 mL, 0.81 mmol). The residue was purified by column chromatography (8:1 hexane/EtOAc) to give compound **1a** (193.1 mg, 91%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.77 (m, 2H), 7.63 – 7.56 (m, 2H), 7.52-7.47 (m, 2H), 7.26-7.23 (m, 5H), 5.10 – 5.06 (m, 1H), 3.94 (td, J = 10.3, 3.7, 1H), 3.48 (t, J = 2.2, 2H), 3.01 (ddt, J = 16.4, 2.4, 1.3, 1H), 2.65 (ddt, J = 16.4, 10.2, 2.5, 1H), 1.71 (d, J = 1.3, 3H), 1.25 (d, J = 1.3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9 (C), 137.59 (C), 136.9 (C), 133.7 (CH), 129.2 (CH), 128.9 (CH), 128.4 (CH), 127.8 (CH), 126.5 (CH), 116.3 (CH), 80.4 (C), 77.3 (C), 63.7 (CH), 25.9 (CH_3), 25.1 (CH_2), 19.2 (CH_2), 18.2 (CH_3); HRMS-ESI *m/z* calcd for $C_{21}H_{22}O_2SNa$ $[M+Na]^+$ 361.1238, found 361.1223.

1-Methoxy-4-(7-methyl-5-(phenylsulfonyl)oct-6-en-2-ynyl)benzene (1b)



1,5-Benzylenyne **1b** was synthesized following the general procedure 1, starting from **4** (200.0 mg, 0.81 mmol) and 1-(chloromethyl)-4-methoxybenzene (0.084 mL, 0.81 mmol). The residue was purified by column chromatography (8:1 hexane/EtOAc) to give compound to yield **1b** (201.8 mg, 88%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.79 (m, 2H), 7.68 – 7.57 (m, 1H), 7.57 – 7.47 (m, 2H), 7.20 – 7.09 (m, 2H), 6.87 – 6.76 (m, 2H), 5.13 – 5.02 (m, 1H), 3.94 (td, J = 10.2, 3.8 Hz, 1H), 3.78 (s, 3H), 3.42 (t, J = 2.4 Hz, 1H), 3.00 (ddt, J = 16.5, 3.8, 2.5 Hz, 1H), 2.64 (ddt, J = 16.5, 10.2, 2.5 Hz, 1H), 1.72 (d, J = 1.3 Hz, 3H), 1.27 (d, J = 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.32 (C), 143.0 (C), 137.7 (C), 133.7 (CH), 129.3 (CH), 129.0 (C), 128.9 (CH), 128.8 (CH), 116.4 (C), 113.9 (CH), 80.9 (C), 77.1 (C), 63.8 (CH), 55.4 (CH_3), 26.0 (CH_3), 24.3 (CH_2), 19.3 (CH_2), 18.3 (CH_3); HRMS-ESI *m/z* calculated for $C_{22}H_{24}O_3SNa$ $[M+Na]^+$ 391.1344, found 391.1331.

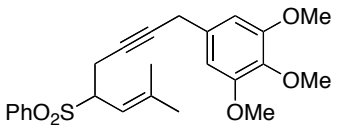
4-(7-Methyl-5-(phenylsulfonyl)oct-6-en-2-yn-1-yl)-1,1'-biphenyl (1c)



1,5-Benzylenyne **1c** was synthesized following the general procedure 1, starting from **4** (100.0 mg, 0.40 mmol) and 4-(chloromethyl)biphenyl (83.2 mg, 0.40 mmol). The residue was purified by column chromatography (8:1 hexane/EtOAc) to give compound **1c** (114.9 mg, 89%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.83 (m, 2H), 7.64 – 7.59 (m, 1H), 7.57 – 7.53 (m, 3H), 7.52 – 7.48 (m, 3H), 7.45 – 7.39 (m, 2H), 7.36 – 7.29 (m, 3H), 5.18-5.04 (m, 1H), 3.96 (td, J = 10.2, 3.8, 1H), 3.53 (t, J = 2.3, 2H), 3.03 (ddt, J = 16.5, 3.7, 2.4, 1H), 2.67 (ddt, J = 16.5, 10.2, 2.6, 1H), 1.73 (d,

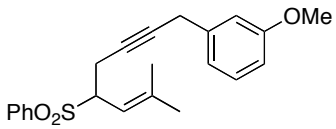
J = 1.3, 3H), 1.27 (d, *J* = 1.3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.11 (C), 140.99 (C), 139.67 (C), 137.73 (C), 136.12 (C), 133.75 (CH), 129.35 (CH), 128.95 (CH), 128.88 (CH), 128.31 (CH), 127.33 (CH), 127.28 (CH), 127.14 (CH), 116.44 (CH), 80.43 (C), 77.52 (C), 63.86 (CH), 26.07 (CH_3), 24.86 (CH_2), 19.35 (CH_2), 18.33 (CH_3); HRMS-ESI *m/z* calcd for $C_{27}H_{26}O_2NaS$ $[M+Na]^+$ 437.1551, found 437.1536.

1,2,3-Trimethoxy-5-(7-methyl-5-(phenylsulfonyl)oct-6-en-2-yn-1-yl)benzene (1d)



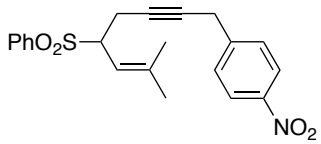
1,5-Benzylenyne **1d** was synthesized following the general procedure 1, starting from **4** (100.0 mg, 0.40 mmol) and ((6-methylhept-5-en-1-yn-4-yl)sulfonyl)benzene (89.1 mg, 0.40 mmol). The residue was purified by column chromatography (4:1 hexane/EtOAc) to give compound **1c** (120.8 mg, 91%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.81 (m, 2H), 7.65 – 7.60 (m, 1H), 7.54 – 7.49 (m, 2H), 6.51 (s, 2H), 5.16 – 5.06 (m, 1H), 3.92 (td, *J* = 9.8, 4.0 Hz, 1H), 3.85 (s, 6H), 3.81 (s, 3H), 3.45 (t, *J* = 2.4 Hz, 1H), 3.00 (ddt, *J* = 16.6, 4.0, 2.4 Hz, 1H), 2.69 (ddt, *J* = 16.6, 9.3, 2.4 Hz, 1H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.23 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3 (C), 142.9 (C), 137.7 (C), 136.8 (C), 133.7 (CH), 132.7 (C), 129.3 (CH), 128.9 (CH), 116.2 (CH), 105.1 (CH), 80.5 (C), 77.3 (C), 63.7 (CH), 60.9 (CH_3), 56.3 (CH_3), 26.0 (CH_3), 25.5 (CH_2), 19.3 (CH_2), 18.2 (CH_3); HRMS-ESI *m/z* calcd for $C_{24}H_{28}O_5SNa$ $[M+Na]^+$ 451.1560, found 451.1555.

1-Methoxy-3-(7-methyl-5-(phenylsulfonyl)oct-6-en-2-yn-1-yl)benzene (1e)



1,5-Benzylenyne **1e** was synthesized following the general procedure 1, starting from **4** (200.0 mg, 0.81 mmol) and *p*-(chloromethyl)anisole (0.121 mL, 0.81 mmol). The residue was purified by column chromatography (4:1 hexane/EtOAc) to give compound **1e** (223.4 mg, 98%) as a yellow sticky solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.82 (m, 2H), 7.67 – 7.56 (m, 1H), 7.56 – 7.46 (m, 2H), 7.18 (t, J = 7.9 Hz, 1H), 6.87 – 6.75 (m, 2H), 6.79 – 6.66 (m, 1H), 5.13 – 5.03 (m, 1H), 3.94 (td, J = 10.2, 3.8 Hz, 1H), 3.77 (s, 3H), 3.46 (t, J = 2.2 Hz, 2H), 3.00 (ddt, J = 16.4, 3.7, 2.5 Hz, 1H), 2.65 (ddt, J = 16.4, 10.1, 2.5 Hz, 1H), 1.71 (d, J = 1.3 Hz, 3H), 1.26 (d, J = 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8 (C), 143.2 (C), 138.6 (C), 137.7 (C), 133.7 (CH), 129.5 (C), 129.3 (CH), 128.9 (CH), 120.2 (CH), 116.3 (CH), 113.9 (CH), 111.7 (CH), 80.4 (C), 63.8 (CH_3), 55.3 (CH), 26.0 (CH_3), 25.2 (CH_2), 19.4 (CH_2), 18.3 (CH_3); HRMS-ESI *m/z* calcd for $C_{22}H_{24}O_3NaS$ $[M+Na]^+$ 391.1344, found 391.1357.

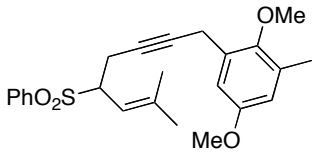
1-(7-Methyl-5-(phenylsulfonyl)oct-6-en-2-yn-1-yl)-4-nitrobenzene (1f)



1,5-Benzylenyne **1f** was synthesized following the general procedure 1, starting from **4** (99.2 mg, 0.40 mmol) and 1-(chloromethyl)-4-nitrobenzene (69.1 mg, 0.40 mmol). The residue was purified by column chromatography (4:1 hexane/EtOAc) to give compound **1f** (88.2 mg, 75%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.10 (m, 2H), 7.85 – 7.81 (m, 2H), 7.66 – 7.60 (m, 1H), 7.52 (t, J = 7.6, 2H), 7.43 (d, J = 8.8, 2H), 5.12 – 5.06 (m, 1H), 3.93 (td, J = 10.0, 4.0, 1H), 3.61 (m, 2H), 3.06 – 2.98 (m, 1H),

2.70 (ddt, *J* = 16.5, 9.8, 2.5, 1H), 1.71 (d, *J* = 1.2, 3H), 1.23 (d, *J* = 1.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7 (C), 143.1 (C), 137.6 (C), 133.8 (CH), 129.3 (CH), 129.0 (CH), 128.7 (CH), 116.43 (CH), 78.9 (C), 78.6 (C), 63.58 (CH), 26.1 (CH_2), 25.2 (CH_3), 19.2 (CH_2), 18.3 (CH_3); HRMS-ESI *m/z* calcd for $C_{21}H_{21}NO_4NaS$ $[M+Na]^+$ 406.1087, found 406.1089.

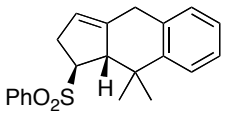
2,5-Dimethoxy-1-methyl-3-(7-methyl-5-(phenylsulfonyl)oct-6-en-2-ynyl)benzene (1g)



1,5-Benzylenyne **1g** was synthesized following the general procedure, starting from **4** (804.0 mg, 3.24 mmol) and 1-(chloromethyl)-2,5-dimethoxy-3-methylbenzene **5** (500.0 mg, 2.49 mmol). The residue was purified by column chromatography (8:1 hexane/EtOAc) to give compound **1g** (1.5 g, 74%) as a orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 2H), 7.60 (d, *J* = 7.5, 1H), 7.50 (t, *J* = 7.6, 2H), 6.76 (d, *J* = 3.0, 1H), 6.57 (d, *J* = 3.0, 1H), 5.05 (dt, *J* = 11.7, 1.4, 1H), 3.93 (dd, *J* = 10.2, 3.7, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.47 (s, 2H), 3.03 – 2.95 (m, 1H), 2.63 (ddt, *J* = 16.4, 10.1, 2.5, 1H), 1.69 (d, *J* = 1.2, 3H), 1.25 (d, *J* = 1.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6 (C), 149.7 (C), 143.1 (C), 137.6 (C), 133.6 (CH), 131.6 (C), 130.9 (C), 129.2 (CH), 128.8 (CH), 116.1 (CH), 114.2 (CH), 112.7 (CH), 80.4 (C), 77.0 (C), 63.7 (CH), 60.4 (CH_3), 55.4 (CH_3), 25.8 (CH_3), 19.6 (CH_2), 19.23 (CH_2), 18.1 (CH_3), 16.3 (CH_3); HRMS-ESI *m/z* calcd for $C_{24}H_{28}O_4NaS$ $[M+Na]^+$ 435.1593, found 435.1606.

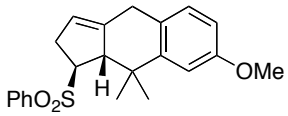
General procedure 2: cyclization of 1,5-benzylenynes. The starting bnezylenyne was dried before the reaction by repeated evaporation of a solution of the compound in toluene (10 mg/mL, 3 times) under vacuum. A solution of the 1,5-benzylenyne in CH_2Cl_2 (0.5-1mL) was added to a solution of the gold(I) complex (5 mol%) in CH_2Cl_2 (0.5 mL) and stirred at room temperature until full conversion (TLC monitoring). The reaction crude was filtered through Celite® and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to provide the cyclized products.

(1*R,9a*S**)-9,9-Dimethyl-1-(phenylsulfonyl)-2,4,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalene (2a)**



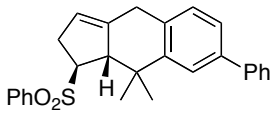
Compound **2a** was synthesized following the general procedure 2 for the cyclization of 1,5-benzylenynes, starting from **1a** (81.3 mg, 0.24 mmol) with catalyst **H**. The residue was purified by column chromatography (10:1 cyclohexane/EtOAc) to give compound **2a** (79.1 mg, 95%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.94 (m, 2H), 7.71 – 7.63 (m, 1H), 7.58 – 7.55 (m, 2H), 7.36 – 7.28 (m, 1H), 7.19 – 7.13 (m, 2H), 7.09 – 7.07 (m, 1H), 5.46 – 5.43 (m, 1H), 3.73 (dt, J = 9.3, 2.4, 1H), 3.61 (br, 2H), 3.22 (br, 1H), 3.11 – 3.01 (m, 1H), 2.80 – 2.66 (m, 1H), 1.18 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5 (C), 138.3 (C), 136.7 (C), 132.8 (C), 132.8 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 125.4 (CH), 125.3 (CH), 118.8 (CH), 63.0 (CH), 54.5 (CH), (C), 38.5 (C), 33.1 (CH_2), 30.7 (CH_2), 25.0 (CH_3), 24.9 (CH_3); HRMS-ESI *m/z* calculated for $C_{21}H_{22}O_2SNa$ $[M+Na]^+$ 361.1238, found 361.1237.

(1*R,9a*S**)-7-Methoxy-9,9-dimethyl-1-(phenylsulfonyl)-2,4,9,9a-tetrahydro-1*H*-cyclopentanaphthalene (2b)**



Compound **2b** was synthesized following the general procedure 2 for the cyclization of 1,5-benzylenynes, starting from **1b** (19.1 mg, 0.05 mmol) with catalyst **T**. The residue was purified by column chromatography (10:1 hexane/EtOAc) to give compound **2b** (18.1 mg, 95%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.90 (m, 2H), 7.67 – 7.61 (m, 1H), 7.54 (t, J = 7.6, 2H), 6.98 (d, J = 8.4, 1H), 6.83 (d, J = 2.6, 1H), 6.72 (dd, J = 8.4, 2.6, 1H), 5.43 – 5.37 (m, 1H), 3.77 (s, 3H), 3.69 (dt, J = 9.3, 2.4, 1H), 3.54 – 3.48 (m, 2H), 3.18 (s, 1H), 3.07 – 2.97 (m, 1H), 2.76 – 2.63 (m, 1H), 1.14 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (C), 146.9 (C), 139.6 (C), 137.8 (C), 133.8 (CH), 130.0 (CH), 129.4 (CH), 129.3 (CH), 126.0 (C), 119.8 (CH), 111.9 (CH), 111.9 (CH), 64.1 (CH), 55.5 (CH_3), 55.4 (C), 39.7 (C), 34.1 (CH_2), 30.9 (CH_2), 26.0 (CH_3), 25.9 (CH_3); HRMS-ESI *m/z* calculated for $C_{22}H_{24}O_3SNa$ $[M+Na]^+$ 391.1344, found 391.1331.

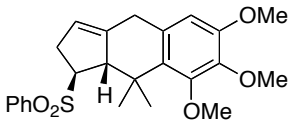
(1*R,9a*S**)-9,9-Dimethyl-7-phenyl-1-(phenylsulfonyl)-2,4,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalene (2c)**



Compound **2c** was synthesized following the general procedure 2 for the cyclization of 1,5-benzylenynes, starting from **1c** (42.3 mg, 0.10 mmol) with catalyst **T**. The residue was purified by column chromatography (10:1 hexane/EtOAc) to give compound **2c** (38.7 mg, 92%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.88 (m, 2H), 7.67 – 7.62 (m, 1H), 7.59 – 7.52 (m, 5H), 7.50 (d, J = 1.7 Hz, 1H), 7.45 – 7.40 (m, 3H), 7.39 – 7.30 (m, 2H), 7.14 (d, J = 7.9 Hz, 1H), 5.46 (s, 1H), 3.73 (dt, J = 9.3, 2.3 Hz, 1H),

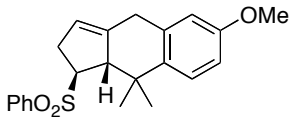
3.63 (s, 2H), 3.24 (s, 1H), 3.06 (d, J = 19.3 Hz, 1H), 2.73 (dd, J = 18.1, 9.1 Hz, 1H), 1.21 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.0 (C), 141.4 (C), 139.5 (C), 139.3 (C), 137.8 (C), 133.8 (CH), 133.1 (C), 129.6 (CH), 129.4 (CH), 129.3 (CH), 128.9 (CH), 127.3 (CH), 127.2 (CH), 125.4 (CH), 125.0 (CH), 120.1 (CH), 64.1 (CH), 55.7 (CH), 39.7 (CH_2), 34.1 (CH_2), 31.5 (CH_2), 26.1 (CH_3), 26.0 (CH_3); HRMS-ESI *m/z* calculated for $C_{27}H_{26}O_2SNa$ $[M+Na]^+$ 437.1551, found 437.1571.

(1*R,9a*S**)-6,7,8-Trimethoxy-9,9-dimethyl-1-(phenylsulfonyl)-2,4,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalene (2d)**



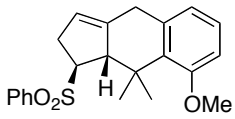
Compound **2d** was synthesized following the general procedure 2 for the cyclization of 1,5-benzylenynes, starting from **1d** (31.8 mg, 0.07 mmol) with catalyst **R**. The residue was purified by column chromatography (8:1 hexane/EtOAc) to give compound **2d** (20.2 mg, 64%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.85 (m, 2H), 7.64 (tt, J = 7.4, 1.1, 1H), 7.54 (t, J = 7.6, 2H), 6.32 (s, 1H), 5.34 (s, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.70 (d, J = 8.9, 1H), 3.50 (d, J = 19.6, 1H), 3.41 (d, J = 18.9, 1H), 3.10 (s, 1H), 3.01 (d, J = 18.9, 1H), 2.70 (dd, J = 17.3, 8.4, 1H), 1.29 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8 (C), 152.0 (C),141.1 (C), 139.4 (C),137.7 (C), 133.8 (CH), 131.2 (C), 130.2 (C), 129.4 (CH), 129.2 (CH), 118.9 (CH), 107.0 (CH), 64.5 (CH), 60.7 (CH_3), 60.6 (CH_3), 57.4 (CH), 55.9 (CH_3), 39.9 (C), 34.2 (CH_2), 32.7 (CH_2), 26.4 (CH_3), 22.6 (CH_3); HRMS-ESI *m/z* calculated for $C_{24}H_{28}O_5SNa$ $[M+Na]^+$ 451.1555, found 451.1554.

(1*R,9a*S**)-6-Methoxy-9,9-dimethyl-1-(phenylsulfonyl)-2,4,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalene (2e)**



Compound **2e** was synthesized following the general procedure 2 for the cyclization of 1,5-benzylenynes, starting from **1e** (46.8 mg, 0.13 mmol) with catalyst **T**. The residue was purified by column chromatography (15:1 cyclohexane/EtOAc) to give compound **2e** (26.7 mg, 57%) as a yellow sticky oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.87 (m, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H), 7.20 (d, J = 8.8 Hz, 1H), 6.71 (dd, J = 8.7, 2.7 Hz, 1H), 6.57 (d, J = 2.7 Hz, 1H), 5.42 (s, 1H), 3.76 (s, 3H), 3.69 (dt, J = 9.3, 2.3 Hz, 1H), 3.56 (s, 2H), 3.16 (s, 1H), 3.07 – 2.98 (m, 1H), 2.70 (dd, J = 18.1, 9.3 Hz, 1H), 1.11 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0 (C), 139.4 (C), 137.9 (C), 137.8 (C), 135.2 (C), 133.8 (CH), 129.4 (CH), 129.2 (CH), 127.2 (CH), 119.8 (CH), 113.3 (CH), 112.7 (CH), 64.1 (CH), 55.8 (CH), 55.3 (CH_3), 38.9 (C), 34.1 (CH_2), 32.0 (CH_2), 26.2 (CH_3), 26.1 (CH_3); HRMS-ESI *m/z* calculated for $C_{22}H_{24}O_3SNa$ $[M+Na]^+$ 391.1344, found 391.1361.

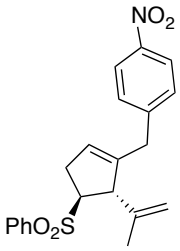
(1*R,9a*S**)-8-Methoxy-9,9-dimethyl-1-(phenylsulfonyl)-2,4,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalene (2e')**



Compound **2e'** was synthesized following the general procedure 2 for the cyclization of 1,5-benzylenynes, starting from **1e** (46.8 mg, 0.13 mmol) with catalyst **T**. The residue was purified by column chromatography (15:1 cyclohexane/EtOAc) to give compound **2e'** (14.4 mg, 31%) as a yellow sticky oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 2H), 7.66 – 7.61 (m, 1H), 7.57 – 7.51 (m, 2H), 7.09 (t, J = 7.9 Hz, 1H), 6.67 (t, J = 8.0 Hz,

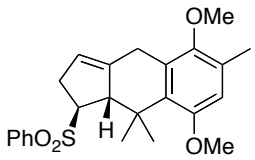
2H), 5.36 – 5.30 (m, 1H), 3.77 (s, 3H), 3.72 (dt, J = 8.8, 1.6 Hz, 1H), 3.54 (d, J = 18.7 Hz, 1H), 3.45 (d, J = 18.7 Hz, 1H), 3.12 (s, 1H), 3.04 – 2.97 (m, 1H), 2.77 – 2.67 (m, 1H), 1.30 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (C), 139.5 (C), 137.7 (C), 136.3 (C),133.7 (CH), 129.4 (CH), 129.2 (CH), 127.0 (CH), 121.8 (CH), 118.8 (CH), 109.4 (CH), 64.7 (CH), 57.7 (CH), 56.3 (C), 55.2 (CH), 40.2 (C), 34.3 (CH_2), 32.6 (CH_2), 25.8 (CH_3), 21.0 (CH_3); HRMS-ESI *m/z* calculated for $C_{22}H_{24}O_3SNa$ [M+Na]$^+$ 391.1344, found 391.1337.

1-Nitro-4-(((4*R*,5R)-4-(phenylsulfonyl)-5-(prop-1-en-2-yl)cyclopent-1-en-1-yl)methyl)benzene (2f)**



Compound **2f** was synthesized following the general procedure 2 for the cyclization of 1,5-benzylenynes, starting from **1f** (48.8 mg, 0.13 mmol) with catalyst **H**. The residue was purified by column chromatography (20:1 hexane/EtOAc) to give compound **2f** (13.2 mg, 26%) as a yellow sticky oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.7 Hz, 2H), 7.92 – 7.76 (m, 2H), 7.62 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 7.9 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 5.34 (s, 1H), 4.86 – 4.59 (m, 1H), 4.49 (s, 1H), 3.72 – 3.55 (m, 1H), 3.52 (s, 1H), 3.41 (d, J = 16.3 Hz, 1H), 3.17 (d, J = 15.2 Hz, 1H), 3.03 – 2.86 (m, 1H), 2.71 (ddt, J = 18.3, 9.5, 2.3 Hz, 1H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 146.5 (C), 142.9 (C), 142.0 (C), 138.0 (C), 133.8 (CH), 130.0 (CH), 129.3 (CH), 128.9 (CH), 126.2 (CH), 123.8 (CH), 117.2 (C), 114.6 (CH2), 66.9 (CH), 56.3 (CH), 35.5 (CH_2), 32.9 (CH_2), 18.8 (CH_3); HRMS-ESI *m/z* calculated for $C_{21}H_{21}NO_4NaS$ [M+Na]$^+$ 406.1089, found 406.1107.

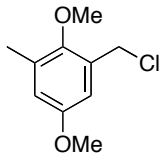
(1*R,9a*S**)-5,8-Dimethoxy-6,9,9-trimethyl-1-(phenylsulfonyl)-2,4,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalene (2g)**



Compound **2g** was synthesized following the general procedure 2 for the cyclization of 1,5-benzylenynes, starting from **1g** (1.3 g, 3.07 mmol) with catalyst **H**. The residue was purified by column chromatography (5:1 hexane/EtOAc) to give compound **2g** (1.2 g, 95%) as a light yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.90 (m, 2H), 7.63 (d, J = 7.0, 1H), 7.54 (dd, J = 8.2, 7.0, 2H), 6.53 (s, 1H), 5.35 (s, 1H), 3.74 (s, 3H), 3.69 (dt, J = 9.0, 2.5, 1H) 3.67 (s, 3H), 3.57 (d, J = 9.7, 1H), 3.51 (d, J = 19.3, 1H), 3.33 (d, J = 19.3, 1H), 3.10 (s, 1H), 3.05 – 2.96 (m, 1H), 2.76 – 2.65 (m, 1H), 2.25 (s, 3H), 1.28 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8 (C), 149.7 (C), 139.8 (C), 137.6 (C), 133.6 (CH), 132.3 (C), 129.7 (C), 129.3 (CH), 129.0 (CH), 128.7 (C), 118.8 (CH), 112.1 (CH), 64.5 (CH_3), 59.6 (CH_3), 57.3 (CH), 55.4 (C), 40.0 (CH_2), 34.2 (CH_2), 27.3 (C), 25.8 (CH_3), 20.9 (CH_3), 16.0 (CH_3); IR (thin film) ν 3066.4 (w), 2928.2 (w), 2867.9 (w), 1601.3 (w), 1446.3 (m), 1297.5 (m), 1281.59 (m), 1234.4 (m), 1141.9 (s), 1087.5 (s), 1087.5 (m) cm^{-1}; HRMS-ESI *m/z* calculated for $C_{24}H_{28}O_4NaS$ [M+Na]$^+$ 435.1606, found 435.1589.

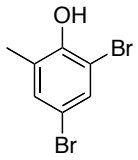
Synthesis of the Benzyl Chloride ***5***

2,5-Dimethoxy-3-methylbenzyl chloride (5)



A solution of freshly distilled thionyl chloride (1.35 mL, 18.04 mmol) in CH_2Cl_2 (3 mL) was added in 30 min at 0 ºC to a solution of benzylalcohol **12** (3.0 g, 16.40 mmol) in CH_2Cl_2 (12 mL) containing Et_3N (2.55 mL, 18.04 mmol). After stirring for 30 min at this temperature the ice bath was removed and the mixture was stirred at rt for 90 min. The mixture was cooled to 0 ºC and quenched with water, diluted with CH_2Cl_2, and washed with water, saturated aqueous sodium hydrogen carbonate, and finally with saturated brine. Removal of the solvent and purification by column chromatography (5% EtOAc) gave the gave the chloride (2.9 g, 88%.) as a orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 3.1, 1H), 6.71 (d, J = 2.8, 1H), 4.63 (s, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.6 (C), 150.5 (C), 132.5 (C), 131.2 (C), 117.4 (CH), 112.8 (CH), 55.5 (CH_3), 44.3 (CH_3), 41.4 (CH_2), 30.8 (CH_3). (NMR data in accordance with those described in literature).[24]

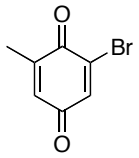
2,4-Dibromo-6-methylphenol (7)



To a solution of *O*-cresol (10.5 mL, 101.00 mmol) in 90% glacial acetic acid in water was added bromine (10.4 mL, 202.00 mmol). The reaction mixture was stirred at room temperature for 1 h then poured into 500 mL of water. The white precipitate was collected by filtration, washed with water

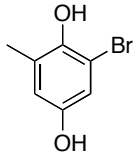
and dried to give the product (25.9 g, 96%) as a white solid: mp 56-57 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 5.56 (s, 1H), 7.19 (s, 1H) and 7.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 110.6, 112.2, 127.8, 131.4, 133.2 and 149.9. (NMR data in accordance with those described in literature).[22]

2-Bromo-6-methylcyclohexa-2,5-diene-1,4-dione (8)



To a suspension containing 2,4-dibromo-6-methylphenol (20.4 g, 77.00 mmol) in 80% acetic acid in water (50 mL) and acetonitrile (25 mL) CrO_3 was added (8.3 g, 83.40 mmol) as a solution in 25 mL of water. The reaction mixture was heated to 60 ºC for 1.5 h, cooled to room temperature, diluted with 400 mL of water and extracted with three 200 mL portions of chloroform. The combined organic layer was washed with two 100 mL portions of brine, dried ($MgSO_4$) and concentrated under diminished pressure to yield the product (14.5 g, 95%) as orange needles: mp 92-94 ºC; ^{1}H NMR (400 Hz$CDCl_3$) δ 2.12 (s, 3H), 6.63 (m, 1H) and 7.20 (d, 1H, J = 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 133.6, 137.5, 138.3, 145.8, 180.1 and 185.0. (NMR data in accordance with those described in literature).[22]

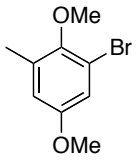
2-Bromo-6-methylbenzene-1,4-diol (9)



A suspension containing 2-bromo- 6-methylcyclohexa-2,5-diene-1,4-dione **8** (12.1 g, 60.20 mmol) in ethanol (120 mL) and water (30 mL) was heated to 50 ºC, and then $Na_2S_2O_4$ (12.6 g, 72.40 mmol) was added. After 2 h the

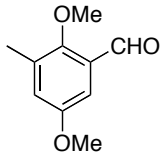
reaction mixture was concentrated under diminished pressure, diluted with 350 mL of ethyl acetate, washed with two 150 mL portions of water, dried ($MgSO_4$) and concentrated under diminished pressure to gave the product (11.6 g, 95%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 4.94 (br s, 1H), 5.20 (s, 1H), 6.60 (d, 1H, J = 2.7 Hz) and 6.82 (d, 1H, J = 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 109.8, 116.0, 117.9, 126.7, 144.9 and 149.1. (NMR data in accordance with those described in literature).[22]

1-Bromo-2,5-dimethoxy-3-methylbenzene (10)



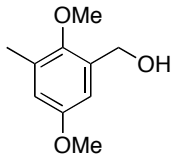
To a solution of 2 bromo-6-methylbenzene-1,4-diol (2.0 g, 9.85 mmol) in acetone (200 mL) dimethylsulfate was added (3.8 mL, 38.00 mmol), and K_2CO_3 (5.5 g, 39.80 mmol). The reaction mixture was heated to reflux for 4 h, cooled to room temperature and filtered. The reaction was followed by GC-MS. The filtrate was concentrated under diminished pressure and redissolved in 200 mL of ethyl acetate, washed with two 100 mL portions of water, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (3:1 hexane–EtOAc) to give the product (1.87, 82%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.74 (s, 3H), 3.76 (s, 3H), 6.67 (d, 1H, J = 3.0 Hz) and 6.92 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 55.9, 60.6, 115.8, 116.3, 117.4, 133.7, 149.5 and 156.1. (NMR data in accordance with those described in literature).[22]

2,5-Dimethoxy-3-methylbenzaldehyde (11)



To a solution containing 1-bromo-2,5-dimethoxy-3-methylbenzene (1.2 g, 5.25 mmol) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (1.03 mL, 6.83 mmol) in anhydrous diethyl ether (30 mL) at -78 ºC under N_2 was added *n*-BuLi 2.5 M in hexane (4.2 mL, 10.50 mmol). The reaction mixture was maintained at -78 ºC for 1 h, then DMF (2.03 mL, 26.3 mmol) was added. The reaction mixture was warmed to room temperature over a period of 1 h, quenched with saturated aq NH_4Cl and diluted with diethyl ether. The reaction was followed by GC-MS. The separated aqueous layer was extracted with two 50 mL portions of diethyl ether. The combined organic layer was washed with one 100 mL portion of brine, one 150 mL portion of water, dried ($MgSO_4$) and concentrated under reduced pressure to give the product (0.9 g, 90%) as a colourless oil which crystallized on standing: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 6.97 (d, 1H, J = 3.3 Hz), 7.11 (d, 1H, J = 3.3 Hz) and 10.31 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 15.7, 55.8, 63.6, 107.7, 125.2, 129.5, 133.9, 155.9, 156.5 and 190.2. (NMR data in accordance with those described in literature).[22]

2,5-Dimethoxy-3-methylbenzyl alcohol (12)

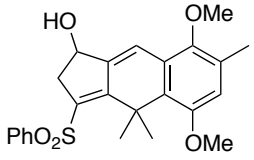


Sodium borohydride (0.4 g, 9.48 mmol) was slowly added to a solution of 2,5-dimethoxy-3-methylbenzaldehyde (0.85 g, 4.74 mmol) in methanol (9.4 mL) at 0 ºC. Reaction mixture was allowed to reach room temperature, stirred for 2 h, and then quenched with 20 mL of diluted aqueous

ammonium chloride. Methanol was evaporated under reduced pressure and aqueous layer was extracted with ether. The ether solution was dried over sodium sulphate and concentrated. Column chromatography of the residue yield desired product (0.7 g, 79%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, J = 3.0, 1H), 6.66 (d, J = 3.0, 1H), 4.69 (s, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 2.84 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.86 (C), 150.2 (C), 134.6 (C), 132.1 (C), 116.0 (CH), 111.4 (CH), 61.4 (CH_3), 61.0 (CH_2), 55.6 (CH_3), 16.2 (CH_3). (NMR data in accordance with those described in literature).[23]

Approach toward Pycnanthuquinone C

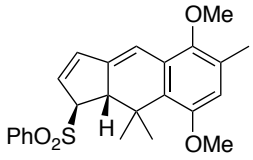
5,8-Dimethoxy-4,4,7-trimethyl-3-(phenylsulfonyl)-2,4-dihydro-1*H*-cyclopenta[*b*]naphthalen-1-ol (14)



To a solution of **2g** (50.0 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was added selenium dioxide (26.9 mg, 0.24 mmol) and the reaction was stirred at room temperature for 2 h. 1 Equivalent of selenium dioxide was added and the reaction was irradiated in the microwave for 45 min at 80-100 ºC. Purification by column chromatography gave the product (26.9 mg, 52%) as a yellow foamy solid: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.94 – 7.92 (m, 2H), 7.63 – 7.60 (m, 1H), 7.58 – 7.54 (m, 2H), 7.12 – 7.11 (m, 1H), 6.73 (s, 1H), 4.76 (d, J = 7.0, 1H), 3.84 (s, 3H), 3.67 (s, 3H), 2.91 (ddd, J = 16.8, 7.5, 0.5, 1H), 2.45 (dd, J = 16.8, 2.1, 1H), 2.26 (d, J = 0.4, 3H), 1.97 (d, J = 6.8, 3H), 1.97 (d, J = 6.8, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 157.9 (C), 153.7 (C), 149.2 (C), 145.4 (C), 141.3 (C), 133.5 (CH), 133.4 (C), 131.7

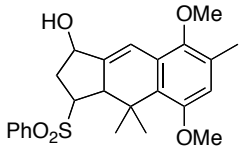
(C), 129.9 (C), 129.5 (CH), 128.3 (CH), 124.7 (C), 122.3 (CH), 115.6 (CH), 69.3 (CH), 61.9 (CH_3), 55.8 (CH_3), 44.3 (CH_2), 39.8 (C), 27.7 (CH_3), 27.5 (CH_3), 15.9 (CH_3); HRMS-ESI *m/z* calculated for $C_{24}H_{26}O_5SNa$ $[M+Na]^+$ 449.1399, found 449.1400.

(1*R,9a*S**)-5,8-Dimethoxy-6,9,9-trimethyl-1-(phenylsulfonyl)-9,9a-dihydro-1*H*-cyclopenta[*b*]naphthalene (16)**



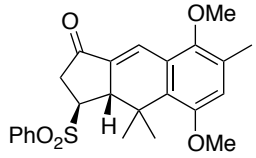
To a solution of **2g** (50.0 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was added at 0 ºC 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (30.9 mg, 0.13 mmol) and the reaction was stirred for 1 h at 0 ºC. Additional DDQ (1.1 equiv) was added and the reaction was stirred for 17 h at room temperature. The solution was filtered through a pad of Celite® and concentrated under vacuum. Purification by column chromatography (4:1 hexane–EtOAc) yielded **16** (59.5 mg, 60%) as a green sticky oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (m, 2H), 7.63 (m, 1H), 7.52 (m, 2H), 6.61 (s, 1H), 6.60 (dd, *J* = 5.6, 1.5, 1H), 6.55 (d, *J* = 2.5, 1H), 6.08 (dd, *J* = 5.5, 2.6, 1H), 4.33 – 4.28 (m, 1H), 3.75 (d, *J* = 4.4, 3H), 3.65 (s, 3H), 3.18 (t, *J* = 2.7, 1H), 2.24 (s, 3H), 1.58 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.3 (C), 144.8 (C), 138.8 (CH), 137.5 (C), 134.0 (CH), 131.5(CH), 129.8 (C), 129.8 (CH), 129.3 (C), 129.2 (CH), 115.1 (CH), 114.2 (CH), 72.9 (CH), 56.3 (CH_3), 49.6 (CH), 49.6 (CH), 38.7 (C), 27.0 (CH_3). LRMS-ESI *m/z* calculated for $C_{24}H_{26}O_4SNa$ $[M+Na]^+$ 410.53, found 433.10.

5,8-Dimethoxy-4,4,7-trimethyl-3-(phenylsulfonyl)-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-1-ol (17)



To a solution of **2g** (40.6 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) and water (0.5 mL) was added DDQ (75.0 mg, 0.33 mmol) at 0 ºC and the reaction was stirred for 2 h at 0 ºC. The solution was filtered through a pad of Celite® and concentrated under vacuum. Purification by column chromatography (4:1 hexane–EtOAc) yielded **17** (18.0 mg, 43%) as a yellow sticky solid: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.96 – 7.94 (m, 2H), 7.72 – 7.69 (m, 1H), 7.64 – 7.60 (m, 2H), 6.85 (d, J = 3.0 Hz, 1H), 6.61 (s, 1H), 4.60 (dd, J = 11.8, 5.7 Hz, 1H), 4.13 (d, J = 12.0 Hz, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 3.60 (dd, J = 9.5, 3.0 Hz, 1H), 3.38 (s, 1H), 2.47 (d, J = 16.1 Hz, 1H), 2.24 – 2.18 (m, 4H), 1.18 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 154.3 (C), 149.7 (C), 144.3 (C), 137.5 (C), 134.6 (CH), 130.1 (C), 129.9 (CH), 129.7 (CH), 129.3 (C), 128.4 (C), 118.9 (CH), 115.4 (CH), 73.8 (CH), 66.5 (CH), 63.4 (CH_3), 56.1 (CH_3), 50.0 (CH), 39.0 (C), 38.0 (CH_2), 25.5 (CH_3), 18.8 (CH_3), 16.0 (CH_3); HRMS-ESI *m/z* calculated for $C_{24}H_{28}O_5SNa$ $[M+Na]^+$ 451.1555, found 451.1571.

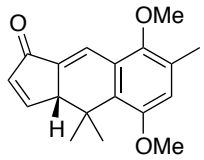
(3*R,3a*R**)-5,8-Dimethoxy-4,4,7-trimethyl-3-(phenylsulfonyl)-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-1-one (18)**



To a solution of **2g** (20.0 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) and a buffer solution (0.05 mL) DDQ was added (37.1 mg, 0.16 mmol) at 0 ºC and the reaction was stirred for 3.5 h at 0 ºC. The solution was filtered through a pad of Celite® and concentrated under vacuum. Purification by column

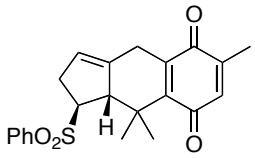
chromatography (4:1 hexane–EtOAc) yielded **18** (3.1 mg, 15%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 7.89 (m, 2H), 7.79 – 7.64 (m, 1H), 7.59 (dd, J = 8.4, 7.0 Hz, 2H), 7.52 (d, J = 3.1 Hz, 1H), 6.79 (s, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.56 (t, J = 3.1 Hz, 1H), 2.99 (dd, J = 19.4, 2.6 Hz, 1H), 2.64 (ddd, J = 19.3, 10.2, 1.1 Hz, 1H), 2.27 (s, 3H), 1.56 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0 (C), 154.2 (C), 137.3 (C), 134.0 (CH), 133.9 (C), 131.1 (C), 130.5 (C), 129.6 (CH), 129.4 (CH), 127.0 (CH), 126.9 (C), 118.5 (CH), 62.8 (CH), 59.1 (CH_3), 56.2 (CH_3), 47.9 (CH), 41.4 (C), 39.9 (CH_2), 24.8 (CH_3), 18.8 (CH_3), 16.0 (CH_3); HRMS-ESI *m/z* calculated for $C_{24}H_{26}O_5SNa$ $[M+Na]^+$ 449.1399, found 449.1395.

5,8-Dimethoxy-4,4,7-trimethyl-3a,4-dihydro-1*H*-cyclopenta[*b*]naphthalen-1-one (18')



To a solution of **2g** (15.5 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) and water (0.05 mL) were added DDQ (28.7 mg, 0.12 mmol) and MnO_2 (11.9 mg, 0.12 mmol). The reaction was stirred at 40 ºC for 5 h. The solution was filtered through a pad of Celite® and concentrated under vacuum. Purification by column chromatography (10:1 hexane–EtOAc) yielded **18'** (2.1 mg, 20%) as a yellow oil: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.64 (dt, J = 5.9, 1.7 Hz, 1H), 7.56 (t, J = 1.5 Hz, 1H), 6.75 (s, 1H), 6.56 (dd, J = 6.0, 2.4 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 2.29 (s, 3H), 1.26 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7 (C), 157.7 (CH), 154.7 (C), 152.2 (C), 138.9 (CH), 135.0 (C), 130.3 (C), 127.4 (C), 122.3 (CH), 116.9 (CH), 62.4 (CH_3), 56.1 (CH_3), 52.2 (C), 38.5 (C), 26.5 (CH_3), 21.1 (CH_3), 14.3 (CH_3); HRMS-ESI *m/z* calculated for $C_{18}H_{20}O_3Na$ $[M+Na]^+$ 307.1310, found 307.1319.

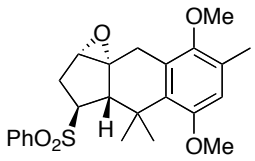
(1*R,9a*S**)-6,9,9-Trimethyl-1-(phenylsulfonyl)-9,9a-dihydro-1*H*-cyclopenta[*b*] naphthalene-5,8(2*H*,4*H*)-dione (20)**



To a solution of **2g** (25.3 mg, 0.06 mmol) and AgO (30.4 mg, 0.25 mmol) in dioxane (1 mL), was added HNO_3 6N (0.1 mL, 0.60 mmol). The reaction was stirred at rt for 1 hour. 10 mL of EtOAc and 10 mL of water were added. The organic phase was extracted with 5 mL portions of water, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by column chromatography (10:1 hexane-EtOAc) to give **20** (11.7 mg, 50%) as a yellow foamy solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (dd, J = 8.3, 1.2, 2H), 7.66 – 7.62 (m, 1H), 7.56 – 7.53 (m, 2H), 6.44 (q, J = 1.2, 1H), 5.43 (t, J = 1.8, 1H), 3.65 (dt, J = 7.3, 1.6, 1H), 3.29 (d, J = 17.4, 1H), 3.07 – 3.00 (m, 2H), 2.99 – 2.92 (m, 1H), 2.68 – 2.62 (m, 1H), 1.99 (d, J = 1.3, 3H), 1.22 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.91 (C), 186.54 (C), 147.38 (C), 144.06 (C), 139.96 (C), 138.96 (C), 135.10 (CH), 133.73 (CH), 129.28 (CH), 129.12 (CH), 66.17 (CH), 64.07 (CH), 63.44 (C), 49.25 (CH), 39.03 (C), 30.29 (CH_2), 25.85 (CH_2), 24.91 (CH_3), 22.81 (CH_3); IR thin film ν 2922.74 (w), 2358.71 (w), 2324.28 (w), 1649.51 (s), 1145 (s) cm^{-1}. HRMS-ESI *m/z* calculated for $C_{22}H_{22}O_4NaS$ $[M+Na]^+$ 405.1137 found 405.1137.

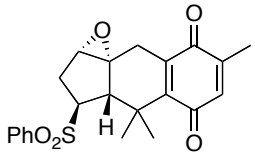
General Procedure 3: Epoxidation. The alkene (1 equiv) was dissolved in CH_2Cl_2 and the solution was cooled down to 0 ºC. *m*-CPBA (2.2 equiv) was then added and the reaction mixture was stirred for 5 hours. The mixture was extracted with $NaHCO_3$, dried with $MgSO_4$ and concentrated under reduced pressure. Purification was made by column chromatography.

(1a*R,3*R**,3a*R**,9a*S**)-5,8-Dimethoxy-4,4,7-trimethyl-3-(phenylsulfonyl)-1a,2,3,3a,4,9-hexahydrobenzo[5,6]indeno[1,7a-*b*]oxirene (21)**



Compound **21** was synthesized following the general procedure 3, starting from **2g** (41.3 mg, 0.0.10 mmol) and *m*-CPBA (49.3 mg, 0.22 mmol) to give **21** (10.5 mg, 25%) as a yellow foamy solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.0, 1.5, 2H), 7.68–7.63 (m, 1H), 7.56–7.51 (m, 2H), 6.57 (s, 1H), 3.78 (s, 3H), 3.66–3.64 (m, 1H), 3.63 (s, 3H), 3.53 (s, 1H), 3.25 (d, *J* = 19.5, 1H), 2.92 (d, *J* = 19.5, 1H), 2.73–2.68 (m, 2H), 2.27 (s, 3H), 2.15 (ddd, *J* = 16.0, 10.1, 1.3, 1H), 1.47 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 154.45 (C), 149.67 (C), 139.27 (C), 133.49 (CH), 130.22 (C), 129.39 (CH), 128.99 (C), 128.88 (CH), 128.04 (C), 112.61 (CH), 67.25 (CH), 64.80 (C), 64.45 (CH_3), 59.56 (CH_3), 55.53 (CH), 50.24 (CH), 39.29 (C), 30.59 (CH_2), 26.59 (CH_3), 26.04 (CH_2), 22.82 (CH_3), 15.93 (CH_3); IR thin film ν 2934.27 (w), 1718.10 (w), 1603.16 (w), 1446.61 (m), 1290.72 (m), 1226.65 (m), 1145.57 (s), 1085.24 (s), 1042.82 (m) cm^{-1}. HRMS-ESI *m/z* calculated for $C_{24}H_{28}O_5NaS$ $[M+Na]^+$ 451.1555, found 451.1543.

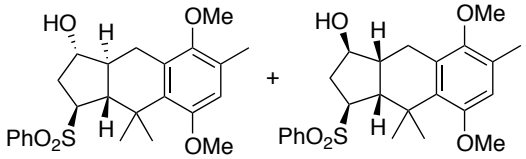
(1a*R,3*R**,3a*R**,9a*S**)-4,4,7-Trimethyl-3-(phenylsulfonyl)-2,3,3a,4-tetrahydrobenzo[5,6]indeno[1,7a-*b*]oxirene-5,8(1a*H*,9*H*)-dione (22)**



Compound **22** was synthesized following the general procedure 3, starting from **20** (11.7 mg, 0.03 mmol) and *m*-CPBA (15.0 mg, 0.07 mmol) to give **22** (3.4 mg, 28%) as a yellow foamy solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ

7.87 (dt, *J* = 8.4, 1.3, 2H), 7.69 – 7.66 (m, 1H), 7.61 – 7.51 (m, 2H), 6.50 (d, *J* = 1.6, 1H), 3.55 (dt, *J* = 10.1, 1.7, 1H), 3.52 (s, 1H), 2.99 (d, *J* = 21.8, 1H), 2.71 (d, *J* = 21.8, 1H), 2.70 (d, *J* = 16.5, 1H), 2.59 (s, 1H), 2.11 (ddd, *J* = 16.0, 10.3, 1.1, 1H), 2.01 (d, *J* = 1.6, 3H), 1.35 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 154.45 (C), 149.67 (C), 139.27 (C), 133.49 (CH), 130.22 (C), 129.39 (CH), 128.99 (C), 128.88 (CH), 128.04 (C), 112.61 (CH), 67.25 (CH), 64.80 (C), 64.45 (CH_3), 59.56 (CH_3), 55.53 (CH), 50.24 (CH), 39.29 (C), 30.59 (CH_2), 26.59 (CH_3), 26.04 (CH_2), 22.82 (CH_3), 15.93 (CH_3); IR thin film ν 2922.74 (w), 2358.71 (w), 2324.28 (w), 1684.13 (s), 1446.68 (w), 1289.32 (m), 1145.87 (s), 1085.36 (s) cm^{-1}. HRMS-ESI *m/z* calculated for $C_{22}H_{22}O_5NaS$ $[M+Na]^+$ 421.1086, found 421.1086.

(3*R,3a*S**)-5,8-Dimethoxy-4,4,7-trimethyl-3-(phenylsulfonyl)-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]naphthalen-1-ol (23) and (1*R**,3*S**,3a*R**,9a*R**)-5,8-dimethoxy-4,4,7-trimethyl-3-(phenylsulfonyl)-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]naphthalen-1-ol (23')**

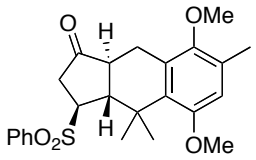


23 **23'**

2g (912.3 mg, 2.21 mmol) was dissolved in dry THF (32.5 mL) under argon. The mixture was cooled down to 0 ºC in an ice-water bath. Borane-tetrahydrofuran complex (7.7 mL, 7.74 mmol) was added dropwise and the temperature of the reaction mixture was kept below 5 ºC. After the addition, the cooling bath was removed and the reaction mixture was allowed to warm to rt and stir for 18 h. To the reaction mixture 4 mL of 3M aqueous sodium hydroxide was added drop wise followed by a 3.6 mL of a solution of 30% hydrogen peroxide solution. The mixture was stirred for 30 min to complete the oxidation process. Sodium bisulfite (4 mL), NaCl (200.0 mg)

and ether (4 mL) were added and the mixture was stirred for 10 min. The organic layer was washed with brine and the water layers were extracted with ether. All the organic layers were combined and dried over anhydrous $MgSO_4$. Filtration, removal of solvent under reduced pressure and purification by column chromatography (10:1 hexane-EtOAc) gave the product (900.0 mg, 95%) as a mixture of diastereoisomers as a white foamy solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.94 (m, 2H), 7.91–7.85 (m, 2H), 7.73–7.51 (m, 7H), 6.60 (s, 1H), 6.56 (s, 1H), 4.20 (t, *J* = 12.5, 2H), 4.04 (dd, *J* = 9.7, 4.8, 1H), 3.80 (d, J = 5.2, 3H), 3.80–3.74 (m, 3H), 3.73 (d, *J* = 4.6, 3H), 3.71–3.63 (m, 6H), 3.61 (s, 3H), 3.59–3.55 (m, 1H), 3.31 (dd, *J* = 16.1, 4.1, 1H), 3.22 (dd, *J* = 10.0, 4.9, 1H), 3.06–3.00 (m, 1H), 3.00–2.86 (m, 2H), 2.71 (dd, *J* = 16.1, 2.4, 1H), 2.53–2.36 (m, 3H), 2.28 (s, 4H), 2.24 (s, 3H), 1.99 (d, *J* = 15.7, 1H), 1.90–1.84 (m, 3H), 1.83–1.68 (m, 4H), 1.50 (s, 3H), 1.43 (dt, *J* = 14.9, 4.7, 4H), 1.33 (d, *J* = 4.8, 6H). HRMS-ESI *m/z* calculated for $C_{24}H_{30}O_5NaS$ $[M+H]^+$ 453.1712, found 453.1720.

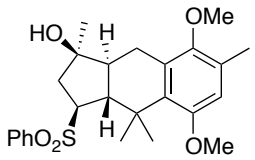
(3*R,3a*S**,9a*R**)-5,8-Dimethoxy-4,4,7-trimethyl-3-(phenylsulfonyl)-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]naphthalen-1-one (24)**



A mixture of diastereoisomers **23** and **23'** (50.6 mg, 0.12 mmol) was dissolved in dry CH_2Cl_2 and DMP (74.8 mg, 0.18 mmol) was added followed by the addition of $NaHCO_3$ (49.4 mg, 0.59 mmol) under argon at 0 ºC. The reaction was stirred at rt for 16 h. A saturated solution of $Na_2S_2O_4$ was added and organic layer was washed with a solution 1:1 of water: saturated $Na_2S_2O_4$. The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by chromatography (4:1 hexane-EtOAc) to give the product (19.8 mg, 40%) as a yellow sticky solid. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.92 (dd, *J* = 5.2, 3.3, 2H), 7.70–7.64 (m,

1H), 7.59 (dd, *J* = 8.2, 6.9, 2H), 6.62 (s, 1H), 3.93 (dt, *J* = 10.0, 8.5, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 3.38 (dd, *J* = 16.7, 4.2, 1H), 2.64–2.57 (m, 1H), 2.51 (dd, *J* = 16.7, 6.4, 1H), 2.47–2.40 (m, 1H), 2.34–2.28 (m, 1H), 2.26 (s, 1H), 2.17 (ddd, *J* = 18.6, 8.3, 1.3, 1H), 1.88 (s, 1H), 1.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210. (C), 154.7 (C), 149.9 (C), 141.9 (C), 139.5 (C), 133.4 (CH), 132.9 (C), 131.9 (C), 129.2 (CH), 128.0 (CH), 112.8 (CH), 60.5 (CH), 59.9 (CH_3), 55.3 (CH_3), 52.9 (CH_2), 48.5 (CH), 42.8 (CH), 38.9 (C), 27.5 (CH_3), 25.5 (CH_2), 20.4 (CH_3), 15.9 (CH_3). HRMS-ESI *m/z* calculated for $C_{24}H_{28}O_5NaS$ $[M+H]^+$ 451.1555, found 451.1559.

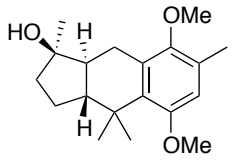
(3*R,3aS*,9a*R**)-5,8-Dimethoxy-1,4,4,7-tetramethyl-3-(phenylsulfonyl)-2,3,3a,4,9, 9a-hexahydro-1*H*-cyclopenta[*b*]naphthalen-1-ol (25)**



Product **24** (15.7 mg, 0.04 mmol) was dissolved in dry THF (1 mL) and cooled down to -100 ºC in an acetone-liquid nitrogen bath. MeLi (0.03 mL, 0.04 mmol) was added dropwising and the mixture was stirred for 16 h from -100 ºC to rt. A solution of saturated NH_4Cl was added and it was extracted with ether. Organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (10:1 hexane-EtOAc) gave the product (5.5 mg, 35%) as a light yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H), 7.68-7.66 (m, 1H), 7.62-7.59 (m, 2H), 6.57 (s, 1H), 4.08 (s, 1H), 3.79 (s, 3H), 7.71 (s, 3H), 3.68-3.64 (m, 1H), 3.05 (dd, *J* = 16.6, 4.0, 1H), 2.77 (dd, *J* = 16.6, 4.0, 1H), 2.68 (dd, *J* = 12.3, 6.3, 1H), 2.26 (s, 3H), 2.24-2.20 (m, 1H), 1.95 (dd, *J* = 15.4, 10.7, 1H), 1.73 (dd, *J* = 12.3, 4.0, 1H), 1.54 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9 (C), 150.5 (C), 138.7 (C), 132.8 (CH), 132.0 (C), 131.3 (C), 129.2 (CH), 128.6 (CH), 128.3 (C), 111.9 (CH), 64.1 (CH), 59.8 (CH_3), 55.3 (CH_3), 53.3 (CH), 44.3 (CH_2),

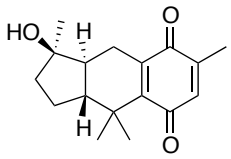
39.0 (C), 27.5 (CH_3), 25.5 (CH_2), 24.4 (CH_3), 20.8 (CH_3), 15.9 (CH_3); IR thin film ν 3474.81 (w), 2919.49 (m), 2849.76 (w), 1704.86 (w), 1447.17 (m), 1396.25 (w), 1301.40 (m), 1301.40 (m), 1142.40 (s), 1083.74 (s), 1039.64 (w) cm^{-1}; HRMS-ESI *m/z* calculated for $C_{25}H_{32}O_5NaS$ $[M+H]^+$ 467.1868, found 467.1870.

(1*R,3a*R**,9a*S**)-5,8-Dimethoxy-1,4,4,7-tetramethyl-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]naphthalen-1-ol (26)**



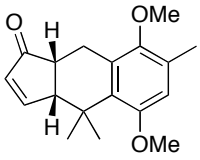
Compound **25** was dissolved in a 1:1 mixture of MeOH-MeCN (3 mL) in the presence of Na(Hg) (129.0 mg, 0.58 mmol) and Na_2HPO_4 (165.0 mg, 1.15 mmol) and was stirred at rt for 1 h. The mixture was diluted with diethyl ether, washed with water and brine, dried (Na_2SO_4) and evaporated under vacuum. Purification by column chromatography (8:1 hexane-EtOAc) gave the product (20.5 mg, 59%) as light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (s, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 2.97 (dd, J = 16.5, 4.8 Hz, 1H), 2.51 (dd, J = 16.5, 12.1 Hz, 1H), 2.26 (s, 3H), 2.13 – 1.92 (m, 1H), 1.91 – 1.71 (m, 3H), 1.69 – 1.56 (m, 2H), 1.52 – 1.46 (m, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2 (C), 145.5 (C), 134.2 (C), 132.0 (C) 128.2 (C), 111.9 (CH), 80.0 (C) 59.8 (CH_3), 55.4 (CH_3), 51.8 (CH), 45.4 (CH), 40.9 (CH_2), 38.0 (C), 27.8 (CH_3), 26.7 (CH3), 24.5 (CH_2), 22.2 (CH_2), 20.6 (CH_3), 16.2 (CH_3); HRMS-ESI *m/z* calculated for $C_{19}H_{28}O_3Na$ $[M+H]^+$ 327.1936, found 327.1938.

(1*R,3a*R**,9a*S**)-1-hydroxy-1,4,4,7-tetramethyl-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]naphthalene-5,8-dione. (Deoxypycnanthuquinone C) (27)**



To a solution of **26** (20.0 mg, 0.07 mmol) and AgO (32.6 mg, 0.26 mmol) in dioxane (1 mL) was added, HNO_3 6N (0.7 μL, 3.94 μmol). The reaction was stirred at rt for 1 hour. 10 mL of EtOAc and 10 mL of water were added. The organic phase was extracted with 5 mL portions of water, dried with $MgSO_4$ and concentrated under reducedpressure. The product was purified by column chromatography (8:1 hexane-EtOAc) to give **27** (10.0 mg, 56%) as a yellow sticky oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (d, J = 1.6 Hz, 1H), 2.66 (dd, J = 19.3, 5.3 Hz, 1H), 2.37 – 2.19 (m, 2H), 2.00 (d, J = 1.6 Hz, 3H), 1.87 – 1.77 (m, 4H), 1.59 – 1.53 (m, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0 (C), 199.1 (C), 149.8 (C), 144.1 (C), 143.4 (C), 134.9 (CH), 79.1 (C), 50.0 (CH), 44.3 (CH), 40.29 (CH_2), 37.7 (C), 21.1 (CH_3), 26.7 (CH_3), 23.8 (CH_2), 21.5 (CH_2), 21.0 (CH_3), 15.28 (CH_3).

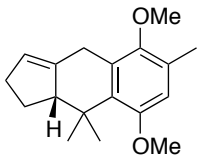
(3a*R,9a*R**)-5,8-Dimethoxy-4,4,7-trimethyl-3a,4,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-1-one (29)**



A mixture of diastereoisomers **23** and **23'** (50.6 mg, 0.12 mmol) was dissolved in dry CH_2Cl_2. DMP (74.8 mg, 0.18 mmol) was added followed by the addition of $NaHCO_3$ (49.4 mg, 0.59 mmol) under argon at 0 ºC. The reaction was stirred at rt for 16 h. A saturated solution of $Na_2S_2O_4$ was added and the organic layer was washed with a solution 1:1 of water:

saturated $Na_2S_2O_4$. The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (4:1 hexane-EtOAc) to give the product (15.7 mg, 18%) as a yellow sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J = 5.8, 2.4, 1H), 6.56 (s, 1H), 6.20 (dd, J = 5.8, 2.2, 1H), 3.71 (s, 3H), 3.60 (s, 3H), 3.21 (dd, J = 15.9, 4.5, 1H), 3.10 (d, J = 8.9, 1H), 2.99 (dt, J = 6.7, 2.3, 1H), 2.80 (m, 1H), 2.23 (s, 3H), 1.53 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (C), 135.2 (CH), 132.6 (C), 129.9 (C), 129.6 (C), 128.6 (C), 113.7 (CH), 112.6 (C), 60.7 (CH_3), 56.0 (CH), 55.0 (CH_3), 44.0 (CH), 38.5 (C), 29.0 (CH_3), 28.5 (CH_3), 23.0 (CH_2), 16.1 (CH_3); IR thin film ν 2929.94 (w), 1702.58 (s), 1462.61 (m), 1398.03 (m), 1302.60 (m), 1232.18 (s), 1144.96 (m), 1084.88 (s), 1021.97 (m) cm^{-1}. HRMS-ESI *m/z* calculated for $C_{18}H_{22}O_3Na$ $[M+H]^+$ 309.1467, found 309.1475.

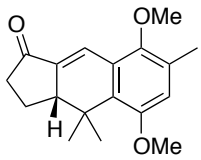
5,8-Dimethoxy-6,9,9-trimethyl-2,4,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalene (30)



Compound **2g** (296.0 mg, 0.72 mmol) was dissolved in a 1:1 mixture of MeOH-MeCN (7 mL) in the presence of Na(Hg) (1.60 g, 7.18 mmol) and Na_2HPO_4 (1.2 g, 8.61 mmol) and was stirred at rt for 2 h. The mixture was diluted with diethyl ether, washed with water and brine, dried (Na_2SO_4) and evaporated under vacuum. Purification by column chromatography 9:1 hexane-EtOAc) gave the product **30** (161.1 mg, 85%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (s, 1H), 5.48 (s, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.60 (d, J = 19.9 Hz, 1H), 3.48 (d, J = 19.7 Hz, 1H), 2.67 (d, J = 9.0 Hz, 1H), 2.40 – 2.30 (m, 2H), 2.26 (s, 3H), 2.10 – 1.91 (m, 2H), 1.50 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3 (C), 150.0 (C), 140.5 (C), 134.4 (C), 130.8 (C), 128.2 (C), 121.4 (CH), 112.1 (CH), 59.8

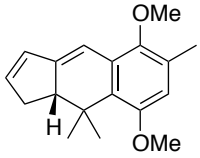
(CH3), 55.7 (CH), 55.6 (CH_3), 40.3 (C), 32.4 (CH_2), 27.6 (CH_2), 27.3 (CH_3), 24.7 (CH_2), 20.7 (CH_3), 16.2 (CH_3); HRMS-ESI *m/z* calculated for $C_{18}H_{25}O_2$ $[M+H]^+$ 273.1849, found 273.1859.

5,8-Dimethoxy-4,4,7-trimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-1-one (31)



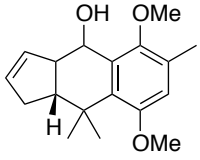
3,5-Dimethylpyrazole (21.0 mg, 0.29 mmol) was added to a suspension of chromium trioxide (38.7 mg, 0.29 mmol) in dry CH_2Cl_2 (0.7 mL) and the mixture was stirred at rt under argon for 15 min. To the resulting dark red solution, compound **30** (21.8 mg, 0.08 mmol) was added in dry CH_2Cl_2 (0.7 mL) in one portion at 0 ºC and the reaction mixture was stirred at rt for 20 hours. The residue was extracted with CH_2Cl_2 and the resulting mixture was filtered through a pad of Celite®. The product was purified by column chromatography (8:1 hexane-EtOAc) to give **31** (17.9 mg, 78%) as light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 3.5 Hz, 1H), 6.76 (s, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 2.89 (ddd, J = 11.2, 7.8, 3.5 Hz, 1H), 2.53 (ddt, J = 18.2, 8.5, 1.3 Hz, 1H), 2.46 – 2.35 (m, 1H), 2.27 (d, J = 0.7 Hz, 3H), 2.23 – 2.10 (m, 1H), 1.93 – 1.73 (m, 1H), 1.64 (s, 3H), 1.58 – 1.54 (m, 1H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) (one C missing) δ 206.9 (C), 154.7 (C), 152.1 (C), 139.4 (C), 136.9 (C), 133.1 (C), 124.2 (CH), 117.7 (CH), 62.5 (CH_3), 56.0 (CH_3), 47.5 (CH), 39.2 (C), 38.5 (CH_2), 27.1 (CH_3), 20.5 (CH_2), 20.1 (CH_3), 15.9 (CH_3); HRMS-ESI *m/z* calculated for $C_{18}H_{23}O_3Na$ $[M+H]^+$ 287.1647, found 287.1653.

5,8-Dimethoxy-6,9,9-trimethyl-9,9a-dihydro-1*H*-cyclopenta[*b*]naphthalene (32)



Compound **30** (45.1 mg, 0.17 mmol) was dissolved in a 2.5 mL of CH_2Cl_2:H_2O. The solution was cooled down to 0 ºC. DDQ (127.0 mg, 0.55 mmol) was added and the reaction was stirred for 2 h. The mixture was filtered through a pad of Celite® and concentrated under vacuum. The product was purified by column chromatography (6:1 hexane-EtOAc) to give **32** (15.2 mg, 35%) as a green sticky oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 6.0, 1.1 Hz, 1H), 7.58 (d, J = 1.1 Hz, 1H), 6.82 (s, 1H), 6.56 (d, J = 6.0 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 2.30 (d, J = 0.7 Hz, 3H), 2.29 – 2.26 (m, 1H), 1.81 – 1.79 (m, 2H), 1.25 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (DEPT 135, 125 MHz, $CDCl_3$) δ 138.8 (CH), 122.7 (CH), 117.9 (CH), 116.3 (CH), 76.7 (CH), 62.5 (CH_3), 56.2 (CH_3), 29.9 (CH_2), 23.6 (CH_3), 21.0 (CH_3), 16.0 (CH_3).

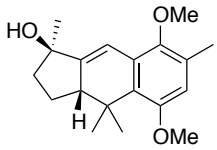
5,8-Dimethoxy-6,9,9-trimethyl-3a,4,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-4-ol (33)



A solution of **30** (89.1 mg, 0.33 mmol) in CH_2Cl_2 (0.4 mL) was added dropwise at rt to a stirred suspension of *t*-butylhydroperoxyde (0.29 mL, 1.18 mmol), selenium oxide (1.8 mg, 0.02 mmol) and salicylic acid (4.6 mg, 0.03 mmol) in CH_2Cl_2 (0.2 mL). The reaction mixture was kept at rt for 30 minutes and quenched with MeOH (0.6 mL) and a 0.2 M solution of NaOH (0.6 mL) at 0 ºC. The solution was stirred at rt for 2 h and then

treated with 15 mL of saturated solution of $NaHCO_3$, water and 30 mL of ether. The aqueous phase was extracted with ether (2x10 mL) and the combined organic phases were washed with 10 mL of a solution of sodium sulfite, followed by brine and dried over $MgSO_4$. The product was purified by column chromatography (20:1 → 4:1 hexane-EtOAc) to give a mixture of diastereoisomers **33** and **33'** (41.6 mg, 44%) as a light yellow oil: Diastereoisomer **33**: ^{1}H NMR (400 MHz, C_6D_6) δ 6.46 (s, 1H), 6.05 (s, 1H), 5.11 (s, 1H), 4.13 (s, 1H), 3.57 (s, 3H), 3.30 (s, 3H), 2.74 (d, J = 7.7 Hz, 1H), 2.37 (d, J = 1.6 Hz, 1H), 2.19 (s, 3H), 2.18 – 2.16 (m, 2H), 1.78 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 155.0 (C), 152.2 (C), 137.1 (C), 134.4 (C), 132.1 (C), 128.9 (C), 114.8 (CH), 79.0 (CH), 73.4 (CH_2), 60.9 (CH_3), 55.0 (CH_3), 38.2 (C), 33.9 (CH_2), 30.5 (CH_2), 25.7 (CH_3), 25.4 (CH_3), 16.3 (CH_3). Diastereoisomer **33'**: ^{1}H NMR (400 MHz, C_6D_6) δ 6.46 (s, 1H), 6.21 (d, J = 1.8 Hz, 1H), 5.48 – 5.25 (m, 1H), 3.74 (s, 3H), 3.49 (d, J = 2.9 Hz, 1H), 3.36 (d, J = 1.1 Hz, 1H), 3.32 (s, 3H), 2.55 (dd, J = 2.7, 1.5 Hz, 1H), 2.34 – 2.27 (m, 1H), 2.28 – 2.24 (m, 1H), 2.21 (s, 3H), 1.75 – 1.72 (m, 4H), 1.64 (s, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 154.1 (C), 152.0 (C), 134.3 (C), 133.5 (C), 128.9 (C), 114.7 (CH), 78.9 (C), 78.1 (CH), 70.1 (CH), 61.1 (CH_3), 60.9 (CH), 55.0 (CH_3), 38.0 (C), 33.3 (CH_2), 28.9 (CH_2), 25.6 (CH_3), 25.1 (CH_3), 16.3 (CH_3).

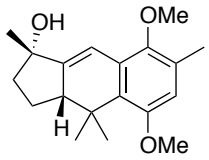
(1*R,3a*S**)-5,8-Dimethoxy-1,4,4,7-tetramethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-1-ol (37)**



Enone **31** (60.0 mg, 0.21 mmol) was dissolved in $LaCl_3 \cdot 2LiCl$ (0.70 mL, 0.42 mmol) under argon. Methylmagnesium bromide (0.13 mL, 0.25 mmol) was added at 0 ºC. The reaction was stirred for 2 min and was quenched with an aqueous solution of NH_4Cl and diluted with diethyl ether. The

product was extracted with ether and the organic layers were washed with brine and dried over $MgSO_4$. Purification by column chromatography (4:1 hexane-EtOAc, 1% Et_3N) gave **37** (15.2 mg, 24%) as a light yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, J = 3.2 Hz, 1H), 6.60 (s, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 2.62 (ddd, J = 9.8, 8.2, 3.3 Hz, 1H), 2.25 (d, J = 0.7 Hz, 3H), 1.95 (ddd, J = 12.6, 5.9, 3.3 Hz, 1H), 1.90 – 1.75 (m, 2H), 1.72 – 1.62 (m, 1H), 1.60 (s, 3H), 1.53 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4 (C), 151.8 (C), 131.5 (C), 129.1 (C), 128.7 (C), 114.2 (CH), 112.6 (CH), 100.1 (C), 78.2 (C), 61.3 (CH_3), 55.9 (CH_3), 50.8 (CH), 41.0 (CH_2), 38.1 (C), 27.4 (CH_3), 26.4 (CH_3), 23.5 (CH_2), 19.6 (CH_3), 16.0 (CH_3); HRMS-ESI *m/z* calculated for $C_{19}H_{26}O_3Na$ $[M+Na]^+$ 325.1774, found 325.1774.

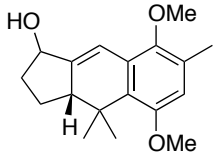
(1*R,3a*R**)-5,8-dimethoxy-1,4,4,7-tetramethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-1-ol (37')**



Enone **31** (60.0 mg, 0.21 mmol) was dissolved in $LaCl_3 \cdot 2LiCl$ (0.70 mL, 0.42 mmol) under argon. Methylmagnesium bromide (0.13 mL, 0.25 mmol) was added at 0 ºC. The reaction was stirred for 2 min and was quenched with an aqueous solution of NH_4Cl and diluted with diethyl ether. The product was extracted with ether and the organic layers were washed with brine and dried over $MgSO_4$. Purification by column chromatography (4:1 hexane-EtOAc, 1% Et_3N) gave **37'** (13.9 mg, 22%) as a light yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, J = 3.3 Hz, 1H), 6.59 (s, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 2.78 (ddd, J = 10.0, 8.1, 3.3 Hz, 1H), 2.25 (s, 3H), 1.94 (ddd, J = 9.9, 7.8, 4.5 Hz, 2H), 1.82 (dd, J = 10.6, 7.2 Hz, 1H), 1.57 (s, 3H), 1.43 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4 (C), 151.6 (C), 149.0 (C), 131.3 (C), 129.2 (C), 128.9 (C), 114.1 (CH), 112.8 (CH),

78.9 (C), 61.3 (CH_3), 56.0 (CH_3), 50.0 (CH), 41.5 (CH_2), 38.1 (C), 27.3 (CH_3), 27.2 (CH_3), 23.1 (CH_2), 19.4 (CH_3), 16.0 (CH_3); HRMS-ESI *m/z* calculated for $C_{19}H_{26}O_3Na$ $[M+Na]^+$ 325.1774, found 325.1774.

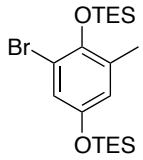
5,8-Dimethoxy-4,4,7-trimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-1-ol (38)



Sodium borohydride (13.2 mg, 0.35 mmol) and cerium trichloride (86.0 mg, 0.35 mmol) were dissolved in MeOH (7 mL) under argon. Compound **31** (40.0 mg, 0.14 mmol) was dissolved in MeOH (3 mL). The mixture was stirred for 10 min at rt and the reaction was quenched with a solution of 10% HCl until neutral pH. Ether and water were added and the organic phase was separated, dried over Na_2SO_4 and the solvent was evaporated unde reduced pressure to give the product (36.6 mg, 91%) as a mixture of diastereoisomers as a yellow oil: Diastereoisomer **38**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (dd, J = 3.2, 1.4 Hz, 1H), 6.60 (s, 1H), 4.74 (s, 1H), 3.89 – 3.78 (m, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 2.56 (td, J = 7.9, 7.4, 3.4 Hz, 1H), 2.26 (s, 3H), 1.97 – 1.78 (m, 4H), 1.60 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6 (C), 149.3 (C), 148.9 (C), 131.5 (C), 129.3 (C), 128.9 (C), 115.4 (CH), 114.5 (CH), 73.9 (CH), 61.5 (CH_3), 56.1 (CH3), 49.9 (CH), 38.2 (C), 35.1 (CH_2), 27.6 (CH_3), 23.5 (CH_2), 19.6 (CH_3), 16.1 (CH_3). Diastereoisomer **38'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (dd, J = 3.4, 2.0 Hz, 1H), 6.60 (s, 1H), 4.68 (t, J = 7.5 Hz, 1H), 3.77 (d, J = 0.8 Hz, 3H), 3.68 (d, J = 0.9 Hz, 3H), 2.72 (ddt, J = 10.8, 7.4, 3.2 Hz, 1H), 2.26 (s, 3H), 2.24 – 2.12 (m, 1H), 2.00 – 1.93 (m, 1H), 1.57 (s, 3H), 1.57 – 1.39 (m, 2H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5 (C), 147.9 (C), 135.2 (C), 129.2 (C), 128.8 (C), 114.8 (CH), 114.2 (CH), 100.1 (C), 75.1 (CH), 61.3 (CH_3), 55.9 (CH3), 49.7 (CH), 38.0 (C), 34.9 (CH_2), 27.3 (CH_3), 22.8

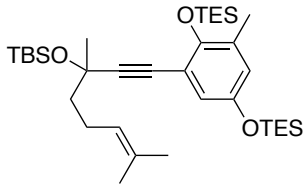
(CH_2), 19.4 (CH_3), 16.0 (CH_3); HRMS-ESI *m/z* calculated for $C_{18}H_{24}O_3Na$ $[M+H]^+$ 311.1623, found 311.1611.

((2-Bromo-6-methyl-1,4-phenylene)bis(oxy))bis(triethylsilane) (47a)



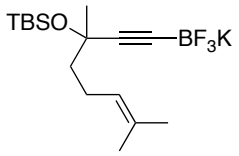
To a suspension of diphenol **9** (1.9 g, 9.65 mmol) in CH_2Cl_2 (15 mL) and triethylamine (4.8 mL, 34.80 mmol) was added triflouromethyl triethylsilanesulfonate (5.24 mL, 23.17 mmol) dropwise over 2 min. During the addition the color change from deep orange to light yellow and the solution was homogenized. The reaction mixture was stirred at rt for 3 hours then quenched with saturated aqueous solution of NH_4Cl (30 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (cyclohexane: CH_2Cl_2 9:1) to give **47a** (2.4 g, 56%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, J = 2.9, 1H), 6.55 (d, J = 2.9, 1H), 2.18 (s, 3H), 1.01 – 0.89 (m, 18H), 0.84 – 0.74 (m, 6H), 0.68 (q, J = 7.9, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7 (C), 146.4 (C), 130.7 (C), 121.8 (CH), 121.6 (CH), 114.8 (C), 18.4 (CH_3), 6.9 (CH_2), 6.7 (CH_2), 5.9 (CH_3), 5.0 (CH_3); HRMS-ESI *m/z* calculated for $C_{19}H_{36}O_2BrSi_2$ $[M+H]^+$ 431.1437, found 431.1430.

((2-(3-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethyloct-6-en-1-yn-1-yl)-6-methyl-1,4-phenylene)bis(oxy))bis(triethylsilane) (48b)



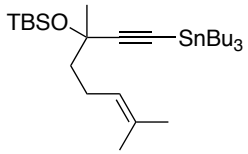
An oven dried Schlenk charged with aryl bromide **47a** (400.0 mg, 0.93 mmol) and 1,6-enyne **54** (687.0 mg, 1.11 mmol) was placed under argon atmosphere. Toluene (9 mL) was then added followed by $Pd(PPh_3)_4$ (214.0 mg, 0.19 mmol) and the reaction was heated to 105 ºC for 16 h. The reaction mixture was cooled down and concentrated under pressure. Purification by column chromatography (5% CH_2Cl_2 in cyclohexane) yielded **48b** (260.0 mg, 46%) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, J = 3.1, 0.7 Hz, 1H), 6.60 (dd, J = 3.1, 0.8 Hz, 1H), 5.15 (tt, J = 7.2, 1.4 Hz, 1H), 2.25 - 2.16 (m, 2H), 2.15 (s, 3H), 1.74 – 1.69 (m, 2H), 1.68 (d, J = 1.4 Hz, 3H), 1.61 (d, J = 1.3 Hz, 3H), 1.52 (s, 3H), 1.01 – 0.91 (m, 18H), 0.89 (s, 9H), 0.85 – 0.75 (m, 6H), 0.74 – 0.64 (m, 6H), 0.22 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.0 (C), 233.8 (C), 128.7 (C), 128.6 (C), 124.5 (CH), 123.2 (CH), 121.8 (CH), 115.6 (C), 96.6 (C), 82.3 (C), 69.8 (C), 45.5 (CH_2), 31.0 (CH3), 30.3 (C), 25.9 (CH_3), 25.8 (CH_3), 23-7 (CH_2), 17.7 (CH_3), 6.9 (CH3), 6.7 (CH_3), 5.9 (CH_2), 5.1 (CH_2), -2.8 (CH_3), -.2.9 (CH_3); HRMS-ESI *m/z* calculated for $C_{35}H_{64}O_3NaSi_3$ $[M+Na]^+$ 639.4061, found 639.4061.

Potassium Trifluoro-(*tert*-butyl((3,7-dimethyloct-6-en-1-yn-3-yl)oxy)dimethylsilane)borate (53)



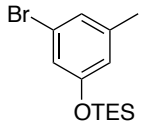
To a solution of 1,6-enyne **46b** (300.0 mg, 1.13 mmol) in THF (2.25 mL) at -78 ºC was added *n*-BuLi (0.45 mL, 1.13 mmol; 2.5 M in hexanes) and the resulting solution was allowed to warm up to -20 ºC and stirred for 1 h. The reaction mixture was cooled down to -78 ºC and triisopropyl borate (0.39 mL, 1.70 mmol) was added. The solution was warmed up to -20 ºC and stirred for 2 h before adding a saturated aqueous solution (1.5 mL) of potassium hydrogen difluoride (528.0 mg, 6.75 mmol) with vigorous stirring. The reaction mixture was allowed to reach rt and stirred further for 1 hour before evaporating to dryness under reduced pressure. Starting material is soluble in CH_2Cl_2 so the solid was washed with a few mL of cold CH_2Cl_2 to remove any remaining. Product is sparingly soluble in most solvents, showed very little solubility in CH_2Cl_2, chloroform or MeOH at rt and required heating to go into acetone or DMSO. The product was extracted from inorganic residues by washing the solid with 3 portions of hot acetone (approx. 20 mL portions at 50 ºC) and filtering the acetone through cotton wool. The acetone extracts were concentrated under reduced pressure and left under vacuum overnight furnishing the desired product **53** (388.0, 93%) as a colorless powder: ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.16 – 5.07 (m, 1H), 2.15 – 2.04 (m, 2H), 1.63 (s, 3H), 1.56 (s, 3H), 1.48 – 1.39 (m, 2H), 1.29 (s, 3H), 0.82 (s, 9H), 0.16 (d, J = 2.2, 6H); ^{19}F NMR (376 MHz, DMSO-d_6) δ -131.67 (s, 3H); HRMS-ESI *m/z* calculated for $C_{16}H_{29}F_3OSiB$ [*M*-K]$^-$ 332.2071, found 332.2075.

tert-Butyl((3,7-dimethyl-1-(tributylstannyl)oct-6-en-1-yn-3-yl)oxy)dimethylsilane (54)



n-BuLi (1.22 mL, 3.04 mmol; 2.5 M in hexanes) was added to a solution of 1,6-enyne **46b** (811.0 mg, 3.04 mmol) in THF (30 mL) at -78 ºC and the resulting mixture was allowed to warm up to -20 ºC and stirred for 1 hour. The reaction mixture was cooled to -78 ºC and tributylchlorostannane (0.83 mL, 3.04 mmol) was added and the mixture was allowed to reach rt and stirred for 16 hour. GC-MS and NMR analysis seemed to indicate complete conversion to the product. The reaction mixture was concentrated under reduced pressure and purified by column chromatography on deactivated silica (cyclohexane) to yield **54** (1.6 g, 90%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 – 5.08 (m, 1H), 2.29 – 2.01 (m, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60 – 1.53 (m, 2H), 1.54 (s, 3H), 1.32 (m, 9H), 1.00 – 0.93 (m, 4H), 0.93 – 0.86 (m, 9H), 0.86 (d, J = 4.9 Hz, 12H), 0.84 – 0.77 (m, 2H), 0.18 (d, J = 1.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.4 (C), 124.8 (CH), 86.1 (C), 72.0 (C), 69.7 (C), 45.7 (CH), 31.7 (C), 29.5 (CH), 29.1 (CH_3), 27.1 (CH_3), 25.9 (CH_2), 25.8 (CH_3), 23.9 (CH_2), 17.7 (CH_3), 13.8 (CH_3), 11.1 (CH_2), 8.9 (CH_2), -2.7 (CH3), -2.9 (CH_3).

(3-Bromo-5-methylphenoxy)triethylsilane (55)

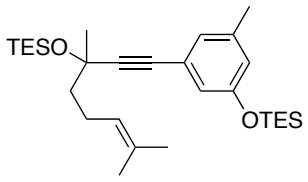


3-Bromo-5-methylphenol (200.0 mg, 1.07 mmol) was dissolved in CH_2Cl_2 (2.1 mL) and cooled to 0 ºC. Triethylamine (298.0 μL, 2.14 mmol) and triethyl(triflurormethoxy)silane (220.0 μL, 1.28 mmol) were added, then the solution was allowed to warm to rt and stirred for 3 h. The reaction

mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 20mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by passing through a short silica column with cyclohexane as eluent (R_f = 0.3) to give **60** (255.0 mg, 79%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (d, J = 1.7 Hz, 1H), 6.81 (t, J = 2.1 Hz, 1H), 6.70 – 6.54 (m, 1H), 2.26 (s, 3H), 1.00 (t, J = 7.9 Hz, 9H), 0.74 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4 (C), 141.0 (C), 125.3 (CH), 122.2 (C), 120.4 (CH), 119.7 (CH), 21.3 (CH_3), 6.71 (CH_3), 5.1 (CH_2); HRMS-ESI *m/z* calculated for $C_{13}H_{22}OSiBr$ $[M+H]^+$ 301.0623, found 301.0622.

General Procedure 4: Sonogashira Cross-Coupling. To a solution of aryl bromide (1 equiv) and 1,6-enyne (1 equiv) in degassed NEt_3, were added sequentially Pd(dppf)Cl_2 (5 mol%) and CuI (10 mol%) at rt under an argon atmosphere. The reaction mixture was stirred for 16 h at 90 ºC on a microwave vial. The reaction was treated with saturated solution of NH_4Cl. The resulting mixture was extracted with EtOAc and the combined organic phases were washed with brine and dried over Na_2SO_4. Purification by column chromatography yielded the desired products.

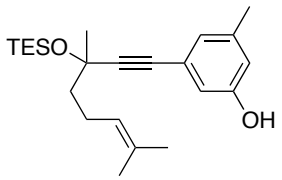
((3,7-Dimethyl-1-(3-methyl-5-((triethylsilyl)oxy)phenyl)oct-6-en-1-yn-3-yl)oxy)triethylsilane (56a)



Compound **56a** was synthesized following the general procedure 4, starting from aryl bromide **55** (50.0 mg, 0.17 mmol), 1,6-enyne **46a** (44.2 mg, 0.17 mmol), Pd(dppf)Cl_2 (6.8 mg, 8.30 μmol) and CuI (3.2 mg, 17.0 μmol) in Et_3N (2 mL). Purification by column chromatography (Cyclohexane → 2%

EtOAc in cyclohexane) gave **56a** (77.0 mg, 86%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 – 6.81 (m, 1H), 6.73 (t, J = 1.7 Hz, 1H), 6.69 – 6.62 (m, 1H), 5.28 – 5.13 (m, 1H), 2.29 (s, 3H), 2.24 (ddd, J = 12.6, 9.1, 6.0 Hz, 2H), 1.77 – 1.73 (m, 2H), 1.72 (d, J = 1.4 Hz, 3H), 1.67 (d, J = 1.3 Hz, 3H), 1.55 (s, 3H), 1.02 (td, J = 7.9, 4.8 Hz, 18H), 0.81 – 0.69 (m, 12H).

3-(3,7-Dimethyl-3-((triethylsilyl)oxy)oct-6-en-1-yn-1-yl)-5-methylphenol (56b)



Compound **56b** was synthesized following the general procedure 4, starting from aryl bromide **59** (176.0 mg, 0.94 mmol), enyne **46a** (376.0 mg, 1.41 mmol), $Pd(dppf)Cl_2$ (38.4 mg, 47.00 μmol) and CuI (38.4 mg, 47.00 μmol) in Et_3N (9 mL). Purification by column chromatography (15:1 cyclohexane-EtOAc) gave **56b** (287.3 mg, 82%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.68 (t, J = 1.8 Hz, 1H), 6.62 (t, J = 1.9 Hz, 1H), 5.25 – 5.09 (m, 1H), 2.28 (s, 3H), 2.27 – 2.14 (m, 2H), 1.77 – 1.67 (m, 2H), 1.70 (s, 3H), 1.64 (s, 3H), 1.53 (s, 3H), 1.00 (t, J = 7.9 Hz, 9H), 0.81 – 0.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3 (C), 140.0 (C), 131.7 (C), 125.1 (CH), 124.4 (CH), 124.3 (C), 116.5 (CH), 115.3 (CH), 93.6 (C), 83.5 (C), 69.5 (C), 45.5 (CH_2), 31.1 (CH_3), 25.9 (CH_3), 23.8 (CH_2), 21.3 (CH_3), 17.8 (CH_3), 7.2 (CH_3), 6.3 (CH_2); HRMS-ESI *m/z* calculated for $C_{23}H_{35}O_2Si$ [*M*-H]$^-$ 371.2406, found 371.2400.

Chapter 3.Gold-Catalyzed Cyclization of Oxo-1,5-Enynes

3.1. Introduction

Among the numerous novel reactions catalyzed by gold, the cycloisomerization of 1,6- and 1,5- enynes shows exceptional versatility. Nucleophilic addition to 1,n-enynes catalyzed by gold complexes as homogeneous catalyst has also been studied extensively. The addition of water or alcohols to 1,6- and 1,5-enynes gives products of hydroxy- or alkoxycyclization.[1,2] The trapping of different intermediates of 1,n-enynes with different nucleophiles allows the formation of complex structures using simple starting materials. The intermolecular addition of to 1,6-enynes takes place also in a stereospecific way. Moreover, the inter- and intramolecular reactions of 1,6-enynes with electron-rich arenes,[3] indoles,[4] 1,3-dicarbonyl compounds,[4] heteroaromatic compounds[3b] and carbonyl groups[5] such as aldehydes or ketones have also been reported. In this

1 (a) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677-1693. (b) Ricard, L.; Gagosz, F. *Organometallics* **2007**, *26*, 4704-4707. (c) Bartolomé, C.; Ramiro, Z.; Pérez-Galán, P.; Bour, C.; Raducan, M.; Echavarren, A. M.; Espinet, P. *Inorg. Chem.* **2008**, *47*, 11391-11397. (d) Chao, C.-M.; Toullec, P. Y.; Michelet, V. r. *Tetrahedron Lett.* **2009**, *50*, 3719-3722. (e) Bartolomé, C.; Ramiro, Z.; García-Cuadrado, D.; Pérez-Galán, P.; Raducan, M.; Bour, C.; Echavarren, A. M.; Espinet, P. *Organometallics* **2010**, *29*, 951-956.

2 Ariafard, A.; Asadollah, E.; Ostadebrahim, M.; Rajabi, N. A.; Yates, B. F. *J. Am. Chem. Soc.* **2012**, *134*, 16882-16890.

3 (a) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genêt, J.-P.; Michelet, V. Angew. Chem. Int. Ed. **2006**, *45*, 7427–7430. (b) Leseurre, L.; Chao, C.-M.; Seki, T.; Genin, E.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Tetrahedron* **2009**, *65*, 1911-1918. (c) Seo, H.; Roberts, B. P.; Abboud, K. A.; Merz, K. M.; Hong, S. *Org. Lett*. **2010**, *12*, 4860–4863.

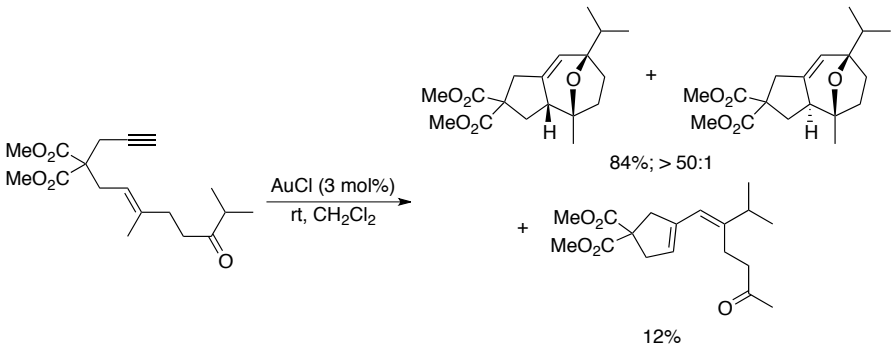
4 Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem*. **2008**, *73*, 7721–7730.

5 (a) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5452-5455. (b) Schelwies, M.; Dempwolff, A. L.; Rominger, F.; Helmchen, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 5598-5601. (c) Schelwies, M.; Moser, R.;

chapter, we have focused our attention in the gold-catalyzed cyclization of enynes with carbonyl groups, in particular to 1,5-enynes.

3.1.1. Gold Catalyzed Addition of Carbonyl Compounds to 1,6-Enynes

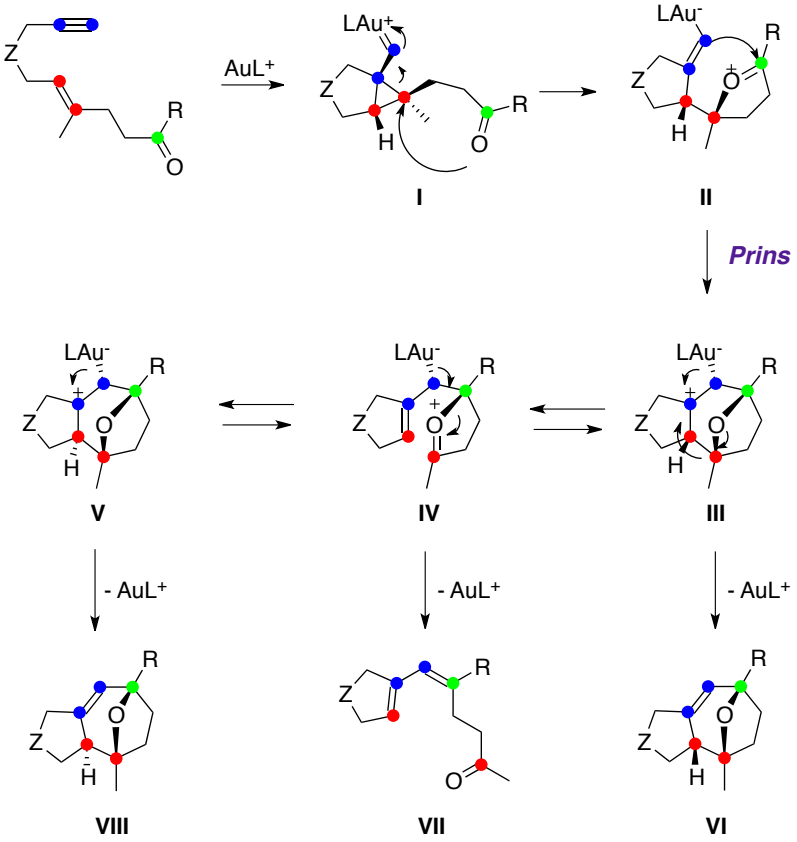
In the gold-catalyzed cyclization of 1,6-enynes bearing a carbonyl group at the alkenyl side chain, this acts as an internal nucleophile leading to oxatricyclic derivatives and rearranged ketones under mild conditions (*Scheme 1*).[5]



Scheme 1. Intramolecular addition of carbonyl groups to 1,6-enynes.

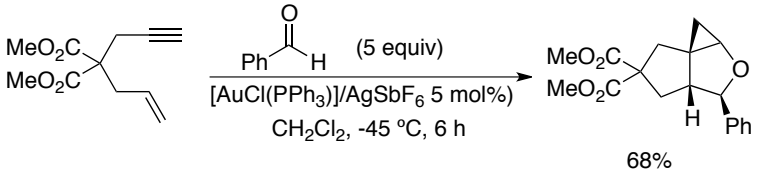
The proposed mechanism of formation of oxatricyclic derivatives takes place through a [2+2+2] alkyne/alkene/carbonyl cycloaddition by a domino process in which two C-C and one C-O bonds are formed. The carbonyl group opens the cyclopropyl gold carbene **I** to form intermediate **II**, which undergoes a Prins cyclization to generate **III**. Finally, metal loss gives tricycle **VI**. Elimination with fragmentation can also occur to form carbonyl compounds **VII**. A competitive 2-oxonia-Cope rearrangement can take place via **IV** and **V** leading to epimer **VIII**.

Dempwolff, A. L.; Rominger, F.; Helmchen, G. *Chem. Eur. J.* **2009**, *15*, 10888-10900. (d) Escribano-Cuesta, A.; López-Carrillo, V.; Janssen, D.; Echavarren, A. M. *Chem. Eur. J.* **2009**, *15*, 5646-5650.



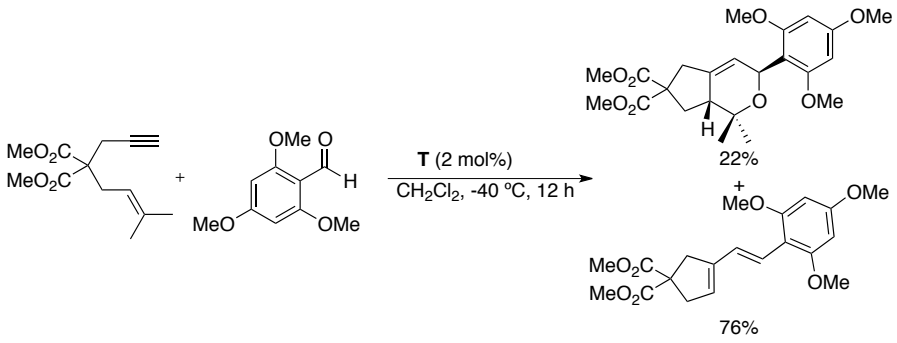
Scheme 2. Proposed mechanism of the intramolecular cycloaddition of 1,6-enynes with carbonyl groups.

The intermolecular reactions between 1,6-enynes bearing a terminal alkyne and carbonyl groups using gold(I)-complexes has also been studied.[5b,c] In this case, reactions proceed with high diastereoselectivity to form 2-oxabicyclo[3.1.0]hexanes following a similar reaction pathway.



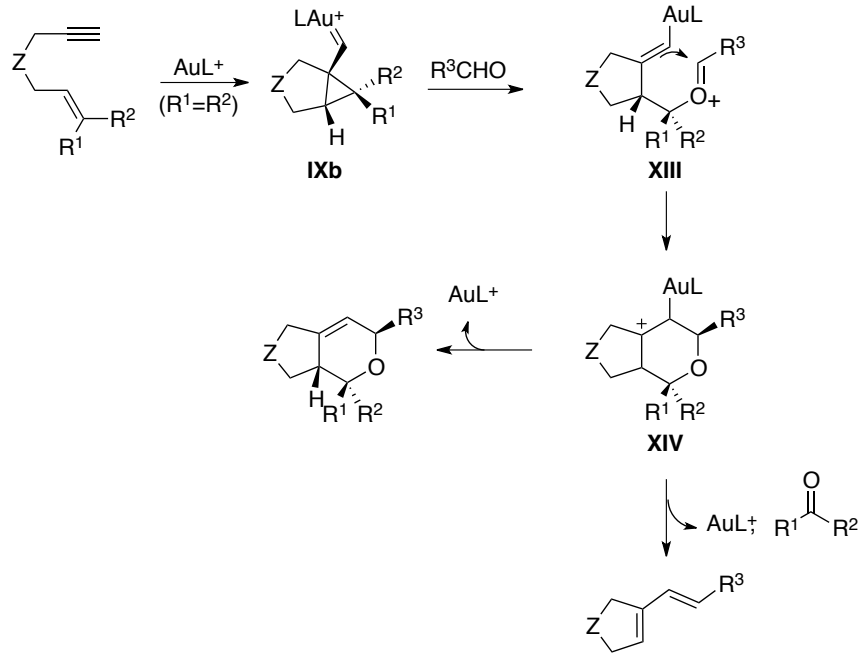
Scheme 3. Intermolecular addition of carbonyls to 1,6-enynes.

A [2+2+2] cycloaddition products have been also observed using 1,6-enynes bearing tertiary substituted alkenes with aldehydes (*Scheme 4*).[5d] However, a formal metathesis also occurs yielding 1,3-dienes as the major products.



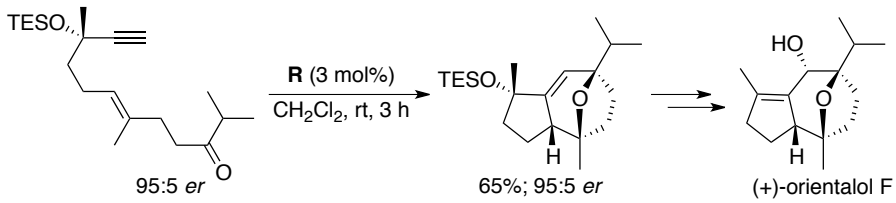
Scheme 4. Intermolecular cyclization of 1,6-enynes with carbonyls.

The mechanism for this reaction is presented in *Scheme 5*.[5d] The aldehyde reacts with cyclopropyl gold(I) carbene **IXb** leading to an oxonium cation **XIII.** Prins cyclization of **XIII** forms tetrahydropyranyl cation **XIV**, which subsequently undergoes elimination of the gold complex to yield the cycloaddition product. A fragmentation reaction of **XIV** leads to 1,3-dienes.



Scheme 5. Mechanism for the intermolecular gold(I)-catalyzed reaction of 1,6-enynes bearing tertiary substituted alkenes with aldehydes.

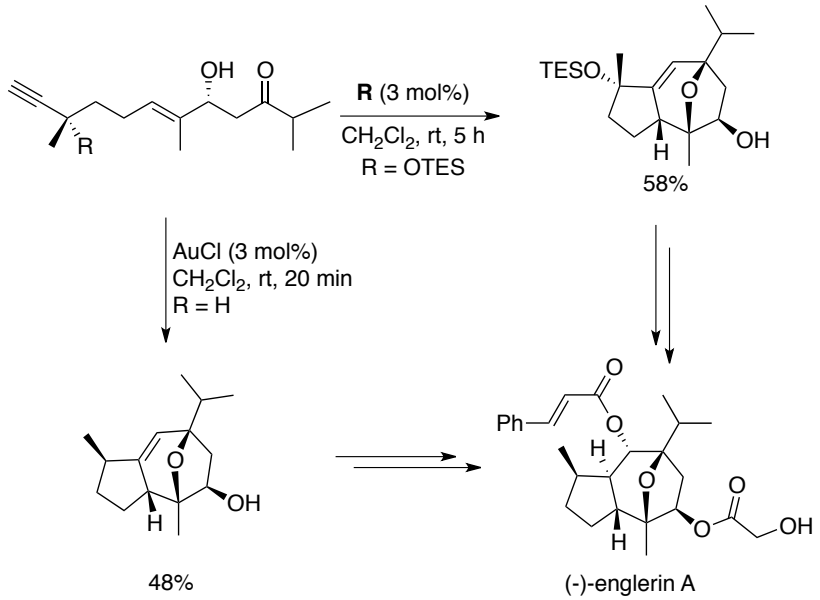
The stereospecific gold(I)-catalyzed intramolecular [2+2+2] alkyne/alkene/carbonyl cycloaddition of ketoenynes was applied to the synthesis of (+)-orientalol F (*Scheme 6*).[6] The synthesis of pubinernoid B was carried out similarly using the *Z* isomer of the starting oxo-1,6-enyne.



Scheme 6. Application the gold(I)-catalyzed intramolecular [2+2+2] cycloaddition reaction in the synthesis of (+)-orientalol F.

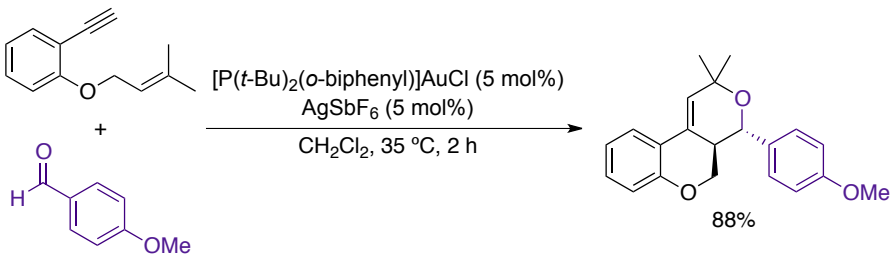
6 Jiménez-Núñez, E.; Molawi, K.; Echavarren, A. M. *Chem. Commun.* **2009**, 7327-7329.

This methodology was also applied for the enantioselective synthesis (-)-englerin A.[7] In a similar approach, AuCl was used as the catalyst for the key cyclization reaction.[8]



Scheme 7. Application in the synthesis of (-)-englerin A.

More recently, an intermolecular [2+2+2]-cycloaddition of 1,7-enynes to carbonyl species has been reported (*Scheme 8*).[9]



Scheme 8. [2+2+2]-Cycloadditions of 1,7-enynes with carbonyl species.

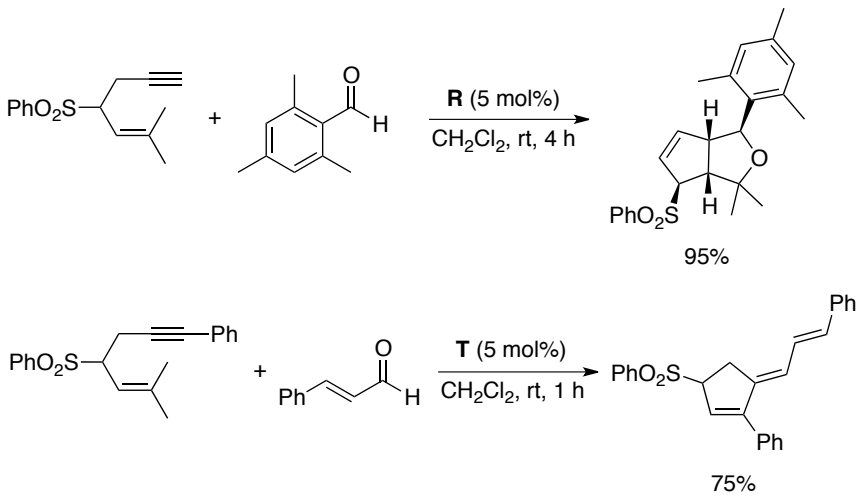
7 Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3517-3519.

8 Zhou, Q.; Chen, X.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 3513-3516.

9 Huple, D. B.; Liu, R.-S. *Chem. Comm.* **2012**, *48*, 10975-10977.

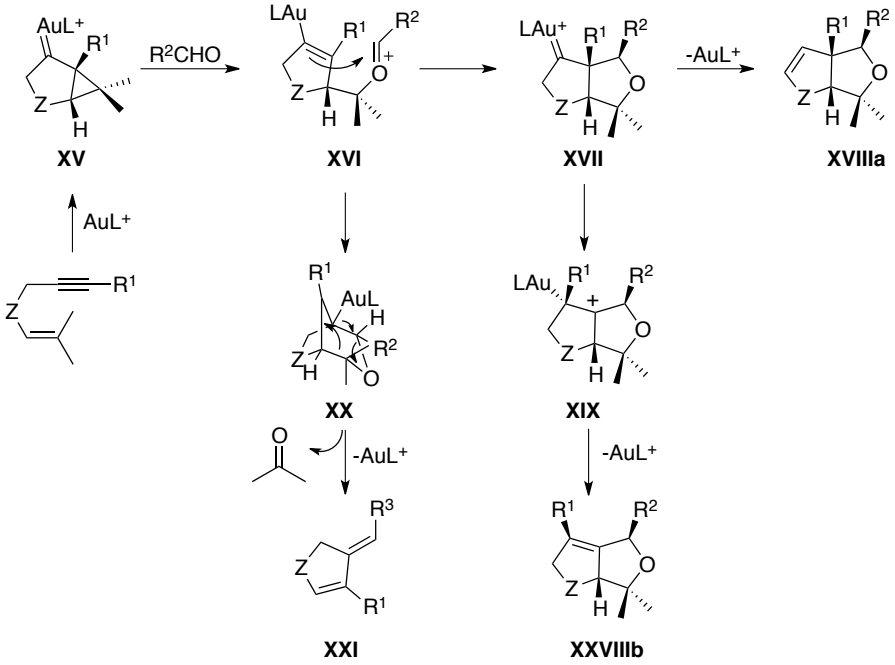
3.1.2. Gold catalyzed addition of carbonyl compounds to 1,5-enynes

Our research group has also examined the intermolecular reaction between carbonyl compounds and 1,5-enynes catalyzed by gold(I).[5d] In this case, bicyclic ethers were obtained as the major product (*Scheme 9*). When 1,5-arylenynes were used as the starting substrates, trienes were obtained as the result of a fragmentation process.



Scheme 9. Gold(I)-catalyzed reaction of 1,5-enynes with carbonyl compounds.

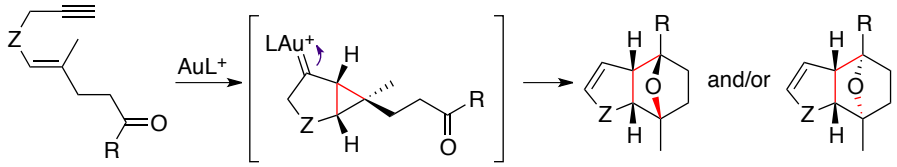
The proposed mechanism of the cycloaddition of 1,5-enynes with carbonyl compounds is similar to the one described previously for 1,6-enynes. Accordingly, addition of the aldehyde to gold carbenes **XV** could form intermediate **XVI**, which undergoes a Prins reaction to give **XVII**. Then, protodemetalation of **XVII** leads to product **XVIIIa**. Alternatively, **XVII** can undergo 1,2-shift of R_1 to yield **XVIIIb**. Intermediate **XVI** can also afford intermediate **XX**. Fragmentation of **XX** would lead **XXI** as product and a molecule of acetone.



Scheme 10. Mechanism for the intermolecular gold(I)-catalyzed reaction of 1,5-enynes with aldehydes.

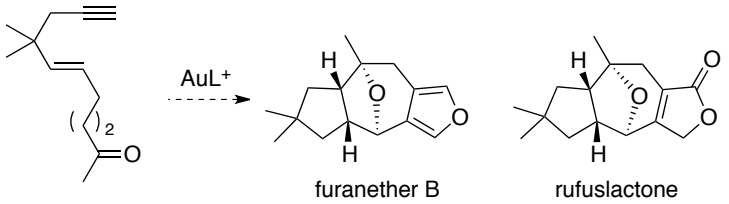
3.2. Objectives

Although the intra- and intermolecular reaction of oxo-1,6-enynes was well known together with the intermolecular reaction of 1,5-enynes,[5] the intramolecular cycloaddition reaction of 1,5-enynes with carbonyl compounds had not been reported. Thus, we decided to investigate the intramolecular reaction of oxo-1,5-enynes in the presence of different gold(I) complexes. In order to propose a consistent mechanism of the reaction, DFT calculations were carried out.



Scheme 11. Intramolecular gold(I)-catalyzed cyclization of oxo-1,5-enynes.

The development of this new methodology was of interest since it could be applied towards the synthesis of natural products such as furanether B, and rufuslactone.[10,11]



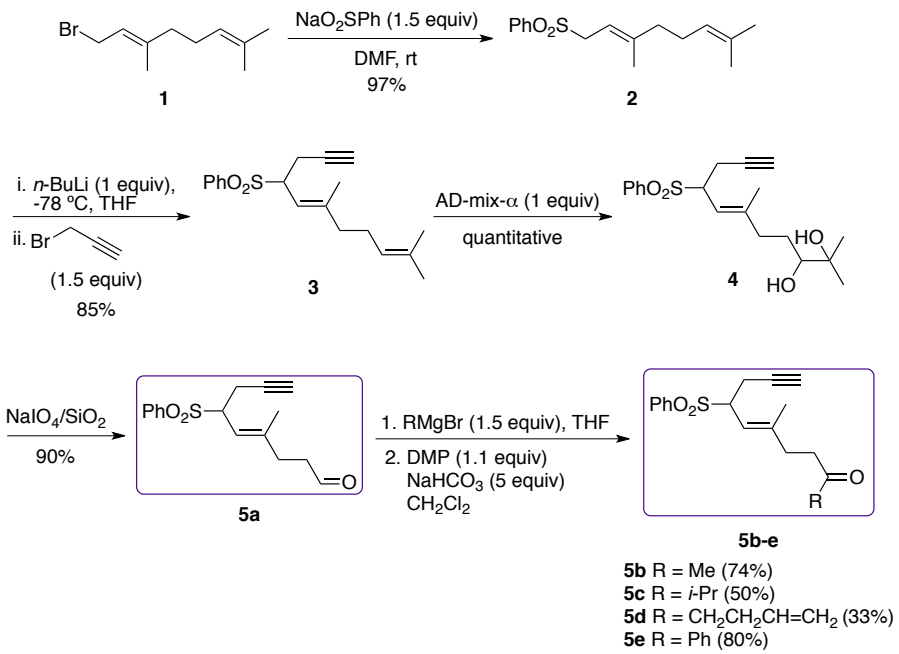
Scheme 12. Proposal towards the synthesis of furanether B and rufuslactone.

10. Luo, D.-Q.; Wang, F.; Bian, X.-Y.; Liu, J.-K. *J. Antibiot.* **2005**, 58, 456-459.

11.Clericuzio, M; Gilardoni, G.; Malagon, O; Vidari, G.; Finzi, P.V. *Nat Prod. Commun.* **2008**, *3*, 951-974.

3.3. Results and Discussion

To study the reactivity of 1,5-enynes bearing a carbonyl group at the alkene side chain in the presence of gold(I)-complexes, oxo-1,5-enynes **6a-e** were synthesized in four to six steps from geranyl bromide (**1**) (*Scheme 13*). Geranyl bromide (**1**) reacted with sodium benzenesulfinate to give sulfone **2** in 97% yield. Deprotonation of **2**, followed by alkylation with propargyl bromide allowed the formation of 1,5-enyne **3** in good yield. Dihydroxylation of **3** with AD-mix-α gave **4** in quantitative yield. Diol **4** then reacted with a suspension of sodium periodate supported in SiO_2[12] to give (*E*)-enynal **5a** in 90% yield. The required substrates **5b-e** were readily prepared via addition of several Grignard reagents, followed by Dess-Martin oxidation (33-80% yields).[13]



Scheme 13. Synthesis of oxo-1,5-enynes **5a-e**.

12 Zhong, Y.; Shing, T. *J. Org. Chem.*, **1997**, *62*, 2622–2624.

13 Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549-7552.

We first examined the cycloaddition of (*E*)-enynal **5a** with cationic gold(I) complexes, which allow the cycloisomerization reactions to be performed under silver(I)-free conditions (*Table 1*). The cyclization proceeded satisfactorily to form oxatricyclic derivatives **6a** and **6a'** through an intramolecular Prins reaction, using gold complexes **H**, **I** and **V** bearing bulky dialkylbiphenylphophine ligands (*Table 1*, entries 1-7) or NHC-Au(I) complex **R** (*Table 1*, entries 9 and 10), whereas lower yields were obtained with catalysts **Q**, **X**, **T**, AuCl, or $AuCl_3$ (*Table 1*, entries 8, 11-14). No cycloisomerization was observed with $NaAuCl_4$, or other metal catalysts as $PtCl_2$, $PtCl_4$, $AgSbF_6$, $GaCl_3$, and $PdCl_2$ (*Table 1*, entries 15-20).

In all cases, besides the expected cyclized derivative **6a**, its stereoisomer **6a'** was also obtained as a minor product with the exception of the reaction using catalyst **T**, which led to the formation of **6a** and **6a'** in a 1:1.5 ratio (*Table 1*, entry 12). Their configurations **6a** and **6a'** were determined by NOESY experiments and were confirmed by the determination of the X-ray structure of **6a'** (*Figure 1*)

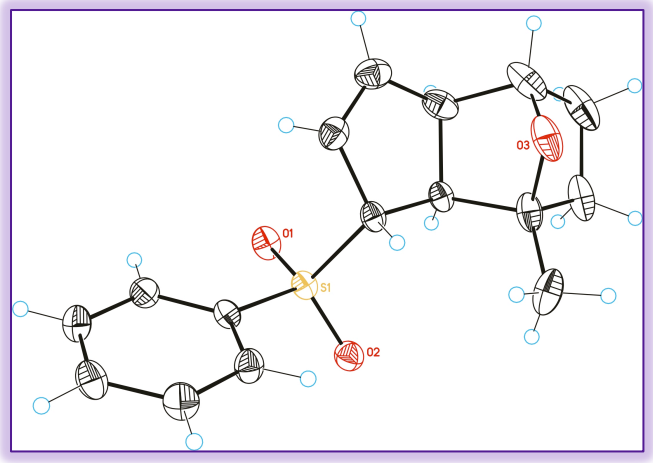
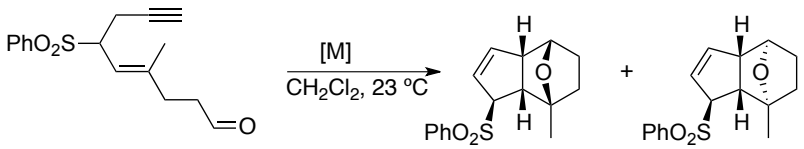


Figure 1. X-ray crystal structure of **6a'**.

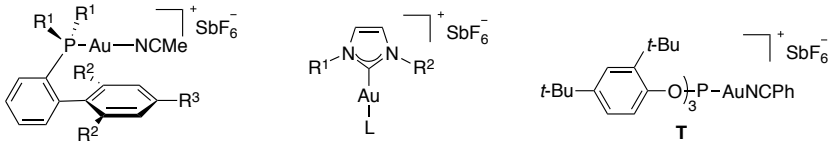
Table 1. Metal-catalyzed cyclization of (*E*)-enynal **5a**.[a]



5a **6a** **6a'**

entry	[M]	time (h)	yield (%)	ratio 6a/6a'
1	**H**	13	54	4.2:1
2[b]	**H**	2	74	4.5:1
3[c]	**H**	0.2	65	5.6:1
4	**I**	14	75	3.6:1
5[b]	**I**	2	78	3.3:1
6	**V**	2	72	3.6:1
7[b]	**V**	2	71	3.1:1
8	**Q**	72	6	2:1
9	**R**	13	64	4:1
10[b]	**R**	2.5	60	4:1
11	**X**	72	16	2:1
12	**T**	7	47	1:1.5
13	AuCl	14	5	4:1[d]
14	$AuCl_3$	14	9	3.5:1[d]
15	$NaAuCl_4$	24	-	-[e]
16	$PtCl_2$	14	-	-[e]
17	$PtCl_4$	14	-	-[e]
18	$AgSbF_6$	14	-	-[e]
19	$GaCl_3$	14	-	-[e]
20	$PdCl_2$	24	-	-[e]

[a] 5 mol% catalyst. Conversion > 93%. [b] 2 mol% catalyst. [c] Reaction at 80 ºC (microwave irradiation). [d] Conversion: 57-61%. [e] **6a**/**6a'** were not detected. The starting material was partially recovered.



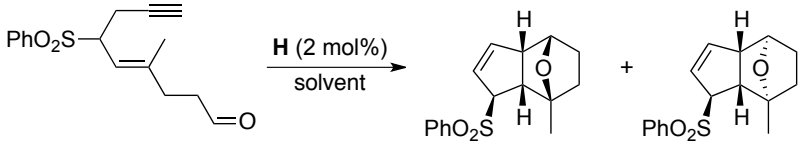
H: R^1 = *t*-Bu, R^2 = R^3 = H
I: R^1 = *t*-Bu, R^2 = R^3 = *i*-Pr
V: R^1 = Cy, R^2 = R^3 = *i*-Pr

Q: R^1 = R^2 = 2,4,6-$Me_3C_6H_2$, L = 2,4,6-$(MeO)_3C_6H_2CN$
R: R^1 = R^2 = 2,6-*i*-$Pr_2C_6H_3$, L = PhCN
X: R^1 = Et, R^2 = Me L = 2,4,6-$(MeO)_3C_6H_2CN$

Figure 2. Additional gold(I) cationic complexes.

As the best results in the cyclization of oxo-1,5-enyne **5a** were obtained using catalyst **H** (*Table 1*, entries 1-3), a series of experiments screening different solvents were carried out with this complex in order to find the optimum conditions.

Table 2. Screening of the solvent with catalyst **H**.



5a **6a** **6a'**

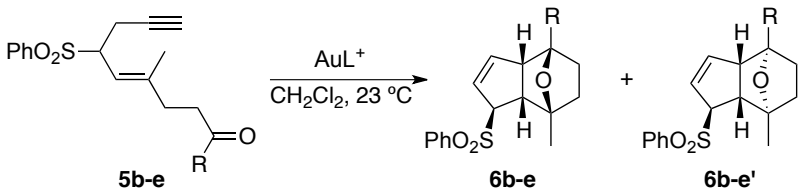
entry	solvent	time	T (ºC)	yield (%)	ratio 6a/6a'
1	toluene	15 h	23	57[a]	4.6:1
2	toluene	10 min	80	55[a]	3.1:1
3	EtOAc	15 h	23	[b]	1:1.4
4	EtOAc	10 min	80	[b]	1:1.3
5	1,4-dioxane	15 h	23	-[c]	-
6	$MeNO_2$	7 d	23	-[d]	-
7	$CHCl_3$	10 min	80	8[a]	2.3:1

[a] Determined by ^{1}H NMR (1,4-diacetylbenzene as internal standard). [b] Yield not determined (quantitative conversion). [c] Complex mixture of different products. [d] **6a**/**6a'** were not detected. The starting material was partially recovered.

As shown in *Table 2*, lower yields were obtained when the reaction was carried out in toluene as solvent (*Table 2*, entries 1-2). Poor results were obtained when the reaction was carried out in $CHCl_3$ (*Table 2*, entry 7). Surprisingly, the use of EtOAc as solvent inverted the selectivity of **6a**/**6a'** to 1:1.4 (*Table 2*, entries 3-4). The reaction did not proceeded satisfactorily in 1,4-dioxane or nitromethane and a complex mixture of products or decomposition of the starting 1,5-enyne was observed (*Table 2*, entries 5-6). Therefore, the optimized conditions found for the cycloisomerization of oxo-1,5-enynes are 2 mol% gold(I) catalyst **H** in the presence of CH_2Cl_2 as solvent and under inert atmosphere (*Table 1*, entry 2).

Different oxo-1,5-enynes **5b-e** bearing substituted ketones were essayed to determine the scope of the reaction (*Table 3*). Methyl ketone **5b** reacted with catalysts **H** and **R** to give excellent yields and moderate selectivities (*Table 3*, entries 1-4). As was found with enyne **5a**, cyclization reaction in the presence of the most electrophilic catalyst **T** led to inversion of the selectivity (*Table 3*, entry 5). 1,5-Enynes **5c-d** also undergo the intramolecular reaction (*Table 3*, entries 6-9). Phenyl ketone **5e** also reacted in the presence of catalyst **H** to give a mixture of products **6e** and **6e'** in a 4:1 ratio and 62% yield (*Table 3*, entry 10). Cationic gold(I) complex **H** was found to be the best catalyst for the cyclization of oxo-1,5-enynes **5b-e**, favoring the formation of **6b-e** over **6b-e'** with moderate selectivities.

Table 3. Scope of the reaction.

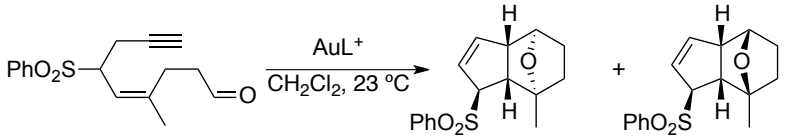


entry	enyne	R	AuL^+	time (h)	yield (%)	ratio 6/6'
1	**1b**	Me	**H**	14	98	3.7:1
2	**1b**	Me	**H**	4	93	3.1:1
3	**1b**	Me	**R**	14	97	3.2:1
4	**1b**	Me	**R**	4	91	3.2:1
5	**1b**	Me	**T**	7	12	1:2.5
6	**1c**	*i*-Pr	**H**	4	51	4:1
7	**1c**	*i*-Pr	**R**	7	32	1.7:1
8	**1d**	$CH_2CH_2CH{=}CH_2$	**H**	2	64	4:1
9	**1d**	$CH_2CH_2CH{=}CH_2$	**H**	2	89	4:1
10	**1e**	Ph	**H**	14	62	4:1

[a] 5 mol% catalyst. Conversion > 99%. [b] 2 mol% catalyst.

We also examined the reactivity of (*Z*)-enynal **7** expecting to form as the major product oxotricycle **6a'** to gain more information about the mechanism of the reaction. Interestingly, the cyclization of **7** proceeded with excellent selectivity to give **6a'** (*Table 4*). Although the best result was obtained using 2 mol% of catalyst **H** (*Table 4*, entry 2), good results were also obtained with catalysts **I**, **R** and **T** (*Table 4*, entries 3-5).

Table 4. Gold-catalyzed cyclization of (*Z*)-enynal **7**.[a]



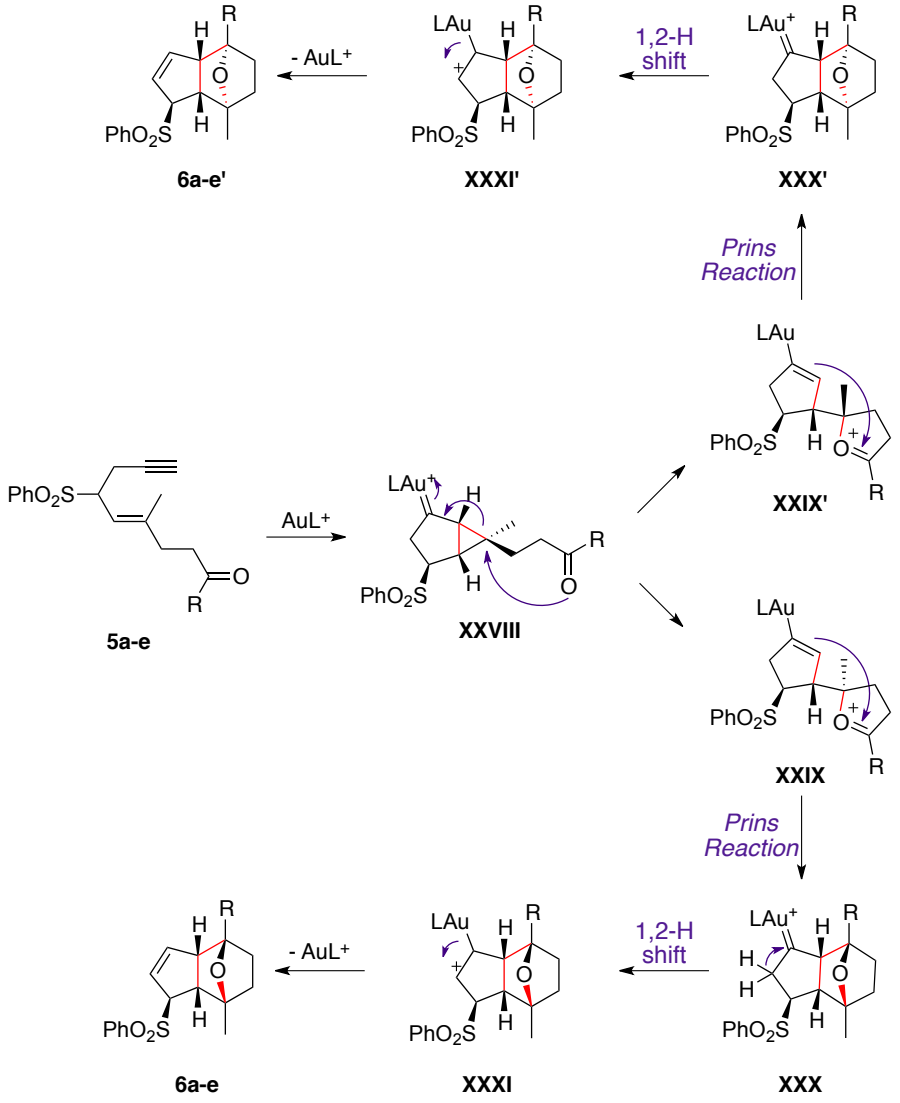
7 **6a'** **6a**

entry	AuL^+	time (h)	yield (%)	ratio 6a'/6a
1	**H**	2	77	20:1
2[b]	**H**	2	97	30:1
3	**I**	4	88	20:1
4	**R**	15	85	20:1
5	**T**	12	65	25:1

[a] 5 mol% catalyst. Conversion > 99%. [b] 2 mol% catalyst.

A mechanistic proposal for this [2+2+2] alkyne/alkene/carbonyl cycloaddition reaction catalyzed by gold(I)-complexes is depicted in *Scheme 14* via cyclopropyl gold(I) carbene **XXVIII**. The carbonyl group acts as an internal nucleophile in **XXVIII** to form oxonium intermediate **XXIX**. Similarly to oxo-1,6-enynes, intermediate **XXIX** could form a second C-C bond by a Prins reaction with the alkenyl metal that, in this case, would give rise to a carbene-like intermediate **XXX**. Thus, intermediate **XXX** would evolve by 1,2-H migration followed by demetallation to form oxatricyclic derivative **6a-e**.

Isomer **6a-e'** could be formed by nucleophilic attack of the carbonyl group on the opposite face to key intermediate **XXIX'**, which differs from **XXIX** in the configuration of the stereocenter present at the 3,4-dihydro-*2H*-furan ring. Then, following the same sequence of reactions, isomer **6a-e'** would be formed.



Scheme 14. Proposed mechanism for the cyclization of oxo-1,5-enyes **5a-e**.

When gold(I) complexes bearing donating ligands were used as catalysts, the major cycloisomerization pathway leads to **6a** and **6a'** from *trans*- and *cis*-substrates respectively, corresponding to a stereospecific process. However, the overall stereoselectivity is not complete, which is consistent with the existence of two competitive processes. In analogy with

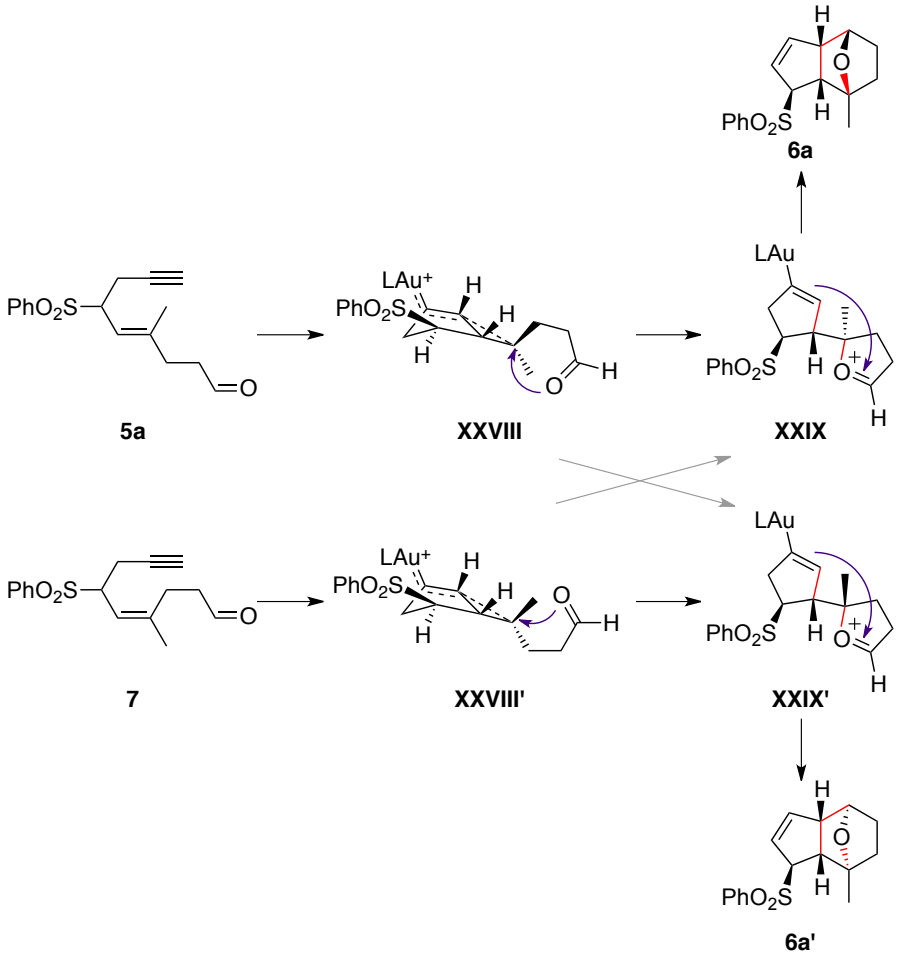
the Stork-Eschenmoser model,[14,15] some gold(I)-catalyzed cascade reactions have been proposed to be concerted.[16] However, the formation of minor stereoisomer **6a'** and **6a** in the cyclization reaction of (*E*)-enynals **5a** and (*Z*)-enynal **7**, respectively, is more consistent with a stepwise process occurring through discrete intermediates such as **XXVIII** and **XXVIII'** (*Scheme 15*), which is in line with other theoretical and experimental results.[17]

14 (a) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helvetica Chimica Acta* **1955**, *38*, 1890-1904. (b) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068-5077. (c) Eschenmoser, A.; Arigoni, D. *Helvetica Chimica Acta* **2005**, *88*, 3011-3050.

15 Stepwise mechanisms might occur in the reaction catalyzed by cyclase enzyme, see: (a) Lodeiro, S.; Xiong, Q.; Wilson, W. K.; Kolesnikova, M. D.; Onak, C. S.; Matsuda, S. P. T. *J. Am. Chem. Soc.* **2007**, *129*, 11213-11222. (b) Gao, J.; Ma, S.; Major, D. T.; Nam, K.; Pu, J.; Truhlar, D. G. *Chem. Rev.* **2006**, *106*, 3188-3209. (c) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730-4756.

16 (a) Fürstner, A.; Morency, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 5030-5033. (b) Böhringer, S.; Gagosz, F. *Adv. Synth. Catal.* **2008**, *350*, 2617-2630. (c) Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276-8277.

17 (a) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269-279. (b) Jiménez-Núñez, E.; Raducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6152-6155. (c) Pérez-Galán, P.; Martin, N. J. A.; Campaña, A. G.; Cárdenas, D. J.; Echavarren, A. M. *Chemistry – An Asian Journal* **2011**, *6*, 482-486.



Scheme 15. Intermediates of the cyclization of oxoenyne **5a** and **7**.

DFT calculations on the formation of the oxatricyclic compounds from both (*E*)- and (*Z*)-enynals correlate qualitatively with the experimental results. As shown in *Figure 3*, the differences in activation energies for the formation of **XXIXa** and **XXIXa'** are 6.66 kcal·mol^{-1} and 11.2 kcal·mol^{-1}, respectively. This is consistent with the selectivity of the reaction of enynal **5a**, which takes place preferentially through $\mathbf{TS_{XXVIIIa\text{-}XXIXa}}$.

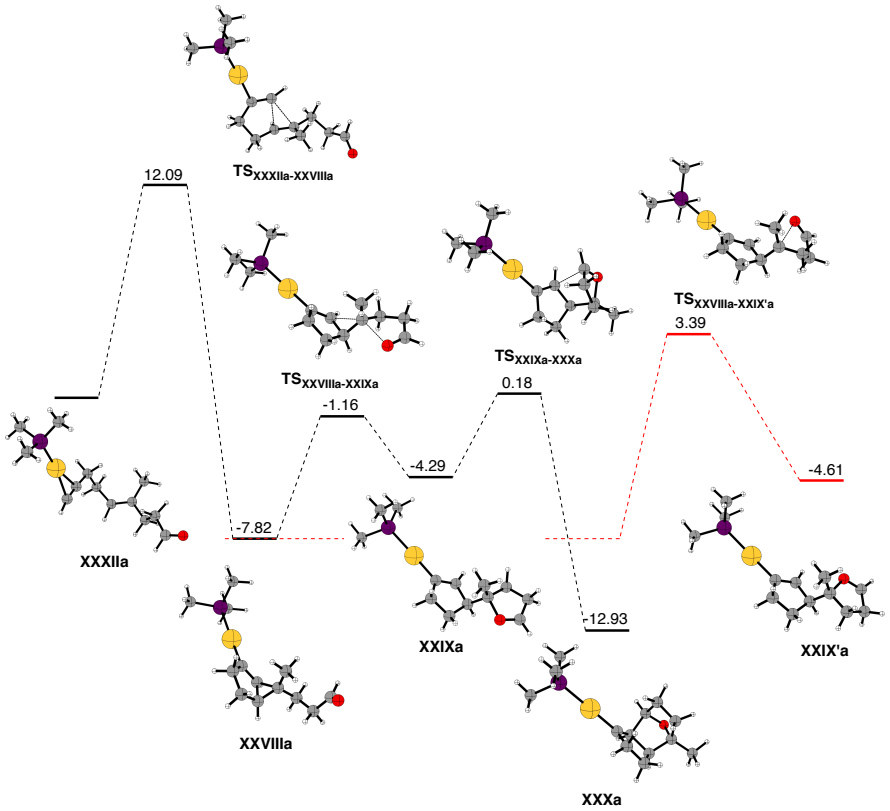


Figure 3. Reaction pathway and energies for the cycloaddition of **XXXIIa** to intermediate **XXIXa** and **XXIX'a**. Calculations at the M06, 6-31G(d) (C, P, H) and SDD (Au) level including solvent effect for CH_2Cl_2. Free energies are given in kcal·mol^{-1}.

In the same manner, *Figure 4* depicts the reaction pathway and energies for the cycloaddition reaction of the (*Z*)-enynal. The differences in activation energies for the formation of **XXIXa'** and **XXIXa** are 8.63 kcal·mol^{-1} and 13.16 kcal·mol^{-1}, respectively. This is in concordance with the experimental results where the major product **6a'** is formed through a lower **TS$_{XXIII'a-XXIVa}$**.

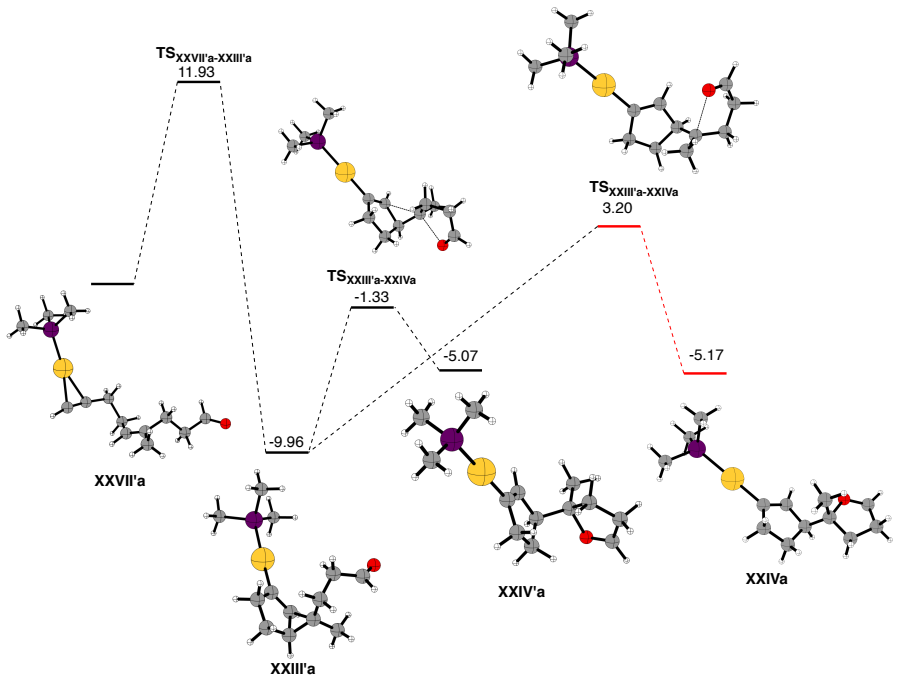


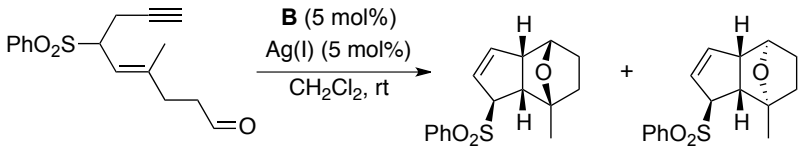
Figure 4. Reaction pathway and energies for the cycloaddition of **XXXII'a** to intermediate **XXIX'a** and **XXIXa**. Calculations at the M06, 6-31G(d) (C, P, H) and SDD (Au) level including solvent effect for CH_2Cl_2. Free energies are given in kcal·mol^{-1}.

Nevertheless, comparing the difference of energies for the cycloaddition of both isomers we should have expected a similar selectivity in both processes although we obtained higher selectivity with isomer *Z* than with the (*E*)-enynal **5a**.

We also decided to study the influence of the counteranion present in the catalyst on the selectivity of the reaction.[18] Thus, different silver salts were tested for the generation of the cationic gold(I) catalyst with enyne **5a** (*Table 5*).

18 This work was carried out in collaboration with Ismael Arroyo, Master student in 2012.

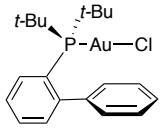
Table 5. Study of the effect of the counteranion in the selectivity of the reaction.



5a **6a** **6a'**

entry	Ag(I) salt	time (h)	yield (%)[a]	ratio 6a/6a'
1	AgOAc	72	SM	-
2	$AgNO_3$	72	decomposition	-
3	$AgCF_3CO_2$	48	decomposition	-
4	$AgSbF_6$	2	45	4:1
5	$AgBF_4$	2	37	2.5:1
6	$AgAsF_6$	0.4	30	1.4:1
7	$AgNTf_2$	2	19	1:3.2
8	AgOTf	1.7	19	1:6
9	$AgPF_6$	2	20	1:1.5

[a] Yields were determined by ^{1}H-NMR using 1,4-diacetylbenzene as internal standard.



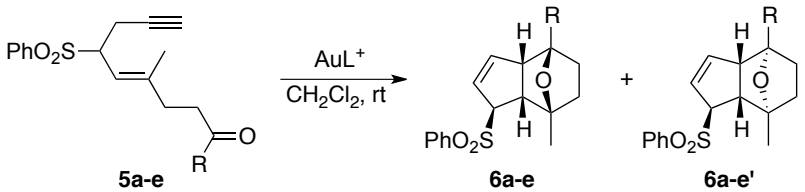
B

The results obtained in the presence of $AgSbF_6$ (*Table 5*, entry 4) are comparable with those obtained with cationic complex **H** (*Table 1*, entry 2). However, the selectivity decreased using $AgBF_4$ or $AgAsF_6$ (*Table 5*, entries 5 and 6). The use of AgOTf (*Table 5*, entry 8) inverted the selectivity of the reaction to 1:6, favoring the formation of **6a'**. However, these results cannot be considered as definitive due to the low yields obtained. Further experiments to investigate the effect of counteranions present in the

selectivity of gold reactions are currently being investigated in our research group.

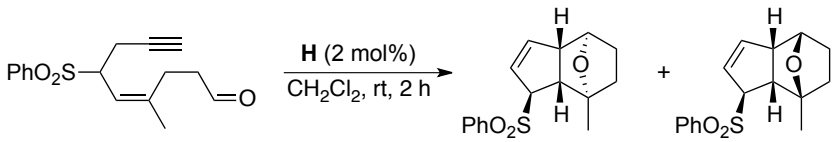
3.4. Conclusions

This work demonstrates that 1,5-enynes bearing a carbonyl group in the alkene side chain react in the presence of gold(I)-catalysts to give oxatricyclic derivatives through a process similar to the one utilizing 1,6-enynes. The mechanism of this tandem process involves a cyclopropanation reaction, an internal nucleophilic attack promoted by the carbonyl compound and a Prins reaction.



5a-e **6a-e** **6a-e'**

While (*E*)-enynals **5a-e** are cyclized with moderate selectivity, the cycloaddition reaction of the *Z* isomer was very selective (30:1).



7 **6a'** **6a**

97%
30:1

The mechanism of this tandem process involves a cyclopropanation reaction, an internal nucleophilic attack promoted by the carbonyl compound and a Prins reaction. The proposed reaction mechanism is supported by DFT calculations.

3.5. Experimental Section

General Procedure

All reactions were carried out under argon in solvents dried using a Solvent Purification System (SPS). Thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck GF234). Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm). NMR spectra were recorded at 23 oC on a Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatus. Mass spectra were recorded on a Waters LCT Premier (ESI) and Waters GCT (EI, CI) spectrometers. IR spectra were performed on a FTIR Bruker Alpha apparatus. Melting points were determined using a Büchi melting point apparatus.

Complex **A**[19] was used as received from Aldrich. The following gold(I) complexes were prepared according to described procedures: **I**,[20] **W**,[21] **T**,[4] **Q**, **R**, and **X**[22].

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

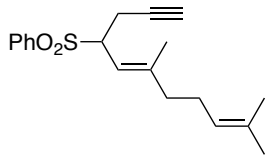
20 Pérez-Galán, P.; Delpont, N.; Herrero-Gómez; Maseras, F.; Echavarren, A. M. *Chem. Eur. J.* **2010**, *16*, 5324-5332.

21 López-Carrillo, V.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 9292-9294.

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

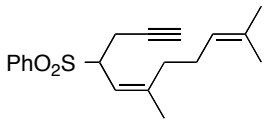
Preparation of Substrates

(*E*)-((6,10-Dimethylundeca-5,9-dien-1-yn-4-yl)sulfonyl)benzene (3)



Over a stirring solution of geranyl bromide (1M) (9.20 mL, 44.0 mmol) in DMF sodium benzylsulfonate (9.04 g, 55.0 mmol) was added at room temperature. The reaction mixture was stirred for 6 h. After extractive work-up (10% HCl solution and Et_2O) the corresponding allylsulfone **2** was isolated and used without further purification. A solution of the allylsulfone **2** in THF was cooled to -78 ºC and *n*-BuLi (17.4 mL, 43.5 mmol, 2.5 M in hexanes) was slowly added. After stirring for 20 minutes propargyl bromide (7.26 mL, 65.2 mmol) was added. The reaction mixture was allowed to warm room temperature and stirred for 14 h (TLC monitoring). The solvent was removed under vacuum and the crude was purified by automated flash chromatography (330 g RediSep flash column, cyclohexane/EtOAc 53 min gradient 0-20% EtOAc) to yield **3** (11.6 g, 85%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 – 7.80 (m, 2H), 7.69 – 7.56 (m, 1H), 7.57 – 7.49 (m, 2H), 5.06 (s, 1H), 5.04 (s, 1H), 3.01 (ddd, J = 16.7, 3.7, 2.7 Hz, 1H), 2.61 (ddd, J = 16.7, 10.1, 2.7 Hz, 1H), 2.00 (br, 4H), 1.94 (t, J = 2.7 Hz, 1H), 1.68 (s, 3H), 1.59 (d, J = 0.8 Hz, 3H), 1.29 (d, J = 1.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.81 (C), 137.52 (C), 133.86 (CH), 132.11 (C), 129.42 (CH), 128.99 (CH), 123.61 (CH), 115.89 (CH), 79.30 (C), 70.86 (C), 63.25 (CH), 39.88 (CH_2), 26.28 (CH_3), 25.82 (CH_3), 18.91 (CH_2), 17.83 (CH_3), 16.71 (CH_3); HRMS-ESI *m/z* calculated for $C_{19}H_{24}O_2SNa$ $[M+Na]^+$ 339.1395, found 339.1389.

(*Z*)-((6,10-Dimethylundeca-5,9-dien-1-yn-4-yl)sulfonyl)benzene (8)



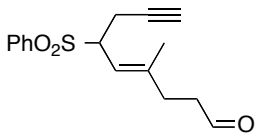
Compound **8** was synthesized from neryl bromide[23] following the procedure described above for the synthesis of (*E*)-((6,10-Dimethylundeca-5,9-dien-1-yn-4-yl)sulfonyl)benzene, starting from neryl bromide (1.37 g, 6.29 mmol), sodium benzylsulfonate (1.29 g, 7.86 mmol), *n*-BuLi (2.85 mL, 4.28 mmol, 1.6 M in hexanes), and propargyl bromide (0.73 mL, 6.42 mmol) to yield **8** (977 mg, 72%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) *d* 7.94 – 7.78 (m, 2H), 7.70 – 7.57 (m, 1H), 7.53 – 7.51 (m, 2H), 5.07 (d, *J* = 10.6 Hz, 1H), 5.01 – 4.90 (m, 1H), 3.97 (td, *J* = 10.2, 3.8 Hz, 1H), 2.97 (ddd, *J* = 16.7, 3.6, 2.9 Hz, 1H), 2.59 (ddd, *J* = 16.7, 10.0, 2.7 Hz, 1H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.91 – 1.75 (m, 3H), 1.72 (d, *J* = 1.3 Hz, 3H), 1.64 (s, 3H), 1.62 – 1.57 (m, 1H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 146.94 (C), 137.48 (C), 133.89 (CH), 132.28 (C), 129.39 (CH), 128.97 (CH), 123.56 (CH), 116.20 (CH), 79.38 (C), 71.07 (CH), 62.98 (CH), 32.33 (CH_2), 26.31 (CH_2), 25.73 (CH_3), 23.65 (CH_3), 19.06 (CH_2), 17.82 (CH_3); HRMS-ESI *m/z* calculated for $C_{19}H_{24}O_2SNa$ $[M+Na]^+$ 339.1395, found 339.1384.

General procedure 1: Synthesis of 4-methyl-6-(phenylsulfonyl)non-4-en-8-ynals. A solution of the corresponding ((6,10-dimethylundeca-5,9-dien-1-yn-4-yl)sulfonyl)benzene (1 equiv) in *tert*-BuOH was added to a stirred solution of AD-mix-α (1 equiv) and methanesulfonamide (1 equiv) in *tert*-BuOH (250 mL) and water (250 mL) at 0 ºC. After stirring the solution over night at room temperature Na_2SO_3 (40.0 g) was added at 0 ºC followed

23 Neryl bromide was prepared from nerol according with the following procedure: Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.*, **2010**, *132*, 14303-14314.

by further stirring for 3 h. The mixture was extracted with EtOAc, the combined organic phases were washed with aq. KOH (2M) and dried over Na_2SO_4. Evaporation of the solvents gave the pure diol as a light yellow oil. To a vigorously stirred suspension of SiO_2-supported $NaIO_4$ [24] in dichloromethane was added a solution of the diol in dichloromethane. After stirring the mixture 1 hour the solids were filtered off over Celite®. Evaporation of the solvents followed by purification by column chromatography on silica gel provided the pure aldehyde.

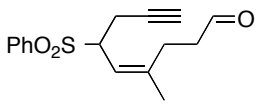
(*E*)-4-Methyl-6-(phenylsulfonyl)non-4-en-8-ynal (5a)



Oxo-1,5-enyne **5a** was synthesized following general procedure 1, starting from (*E*)-((6,10-dimethylundeca-5,9-dien-1-yn-4-yl)sulfonyl)benzene **3** (5.0 g, 15.80 mmol). The residue was purified by column chromatography (3:1 cyclohexane/EtOAc) to give compound **5a** (4.2 g, 92%) as a yellow solid: mp 52 – 54 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (t, J = 1.5 Hz, 1H), 7.97 – 7.73 (m, 2H), 7.69 – 7.60 (m, 1H), 7.56 – 7.52 (m, 3H), 5.08 (ddd, J = 10.3, 2.6, 1.3 Hz, 1H), 3.95 (td, J = 10.2, 3.8 Hz, 1H), 2.98 (ddd, J = 16.7, 3.8, 2.8 Hz, 1H), 2.60 (ddd, J = 16.7, 10.2, 2.7 Hz, 2H), 2.47 (tm, J = 7.5 Hz, 2H), 2.32 (t, J = 7.4 Hz, 2H), 1.94 (t, J = 2.7 Hz, 1H), 1.32 (d, J = 1.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.27 (CHO), 144.80 (C), 137.37 (C), 134.02 (C), 129.33 (CH), 129.28 (CH), 129.13 (CH), 116.85 (CH), 71.11 (CH), 63.03 (CH), 41.66 (CH_2), 31.8 (CH_2), 18.86 (CH_2), 16.83 (CH_3); IR (thin film) ν 3244 (CH terminal alkyne), 1712 (C=O) cm^{-1}; HRMS-ESI *m/z* calculated for $C_{16}H_{18}O_3SNa$ $[M+Na]^+$ 313.0874, found 313.0867.

24 Y. Zhong, T. Shing, *J. Org. Chem*., **1997**, *62*, 2622–2624.

(*Z*)-4-Methyl-6-(phenylsulfonyl)non-4-en-8-ynal (7)



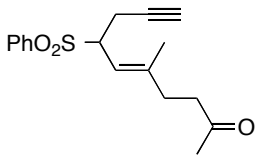
Oxo-1,5-enyne **7** was synthesized following general procedure 1, starting from (*Z*)-((6,10-Dimethylundeca-5,9-dien-1-yn-4-yl)sulfonyl)benzene **8** (3.0 g, 0.98 mmol). The residue was purified by column chromatography (3:1 cyclohexane/EtOAc) to give compound **7** (2.7 g, 86%) as a yellow solid: mp 72 – 75 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.86 – 7.84 (m, 2H), 7.69 – 7.61 (m, 1H), 7.57 – 7.54 (m, 2H), 5.14 (d, J = 10.8 Hz, 1H), 4.01 (td, J = 10.3, 3.7 Hz, 1H), 2.94 (ddd, J = 16.7, 3.6, 2.8 Hz, 1H), 2.59 (ddd, J = 16.7, 10.1, 2.7 Hz, 1H), 2.42 (dddd, J = 14.3, 7.6, 5.1, 0.9 Hz, 1H), 2.26 (dddd, J = 14.4, 7.4, 4.4, 0.9 Hz, 1H), 2.15 – 2.08 (m, 1H), 2.02 (ddd, J = 14.6, 9.5, 5.5 Hz, 1H), 1.96 (t, J = 2.7 Hz, 1H), 1.75 (d, J = 1.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.02 (C), 145.00 (C), 137.44 (C), 134.07 (CH), 129.37 (CH), 129.17 (CH), 117.39 (CH), 79.17 (C), 71.24 (CH), 62.93 (CH), 41.92 (CH_2), 24.39 (CH_2), 23.53 (CH_3), 19.22 (CH_2); IR (thin film) ν 3267 (CH terminal alkyne), 1713 (C=O) cm^{-1}; HRMS-ESI *m/z* calculated for $C_{16}H_{18}O_3SNa$ $[M+Na]^+$ 313.0874, found 313.0863.

General procedure 2: Synthesis of Grignard reagents. Applied to compounds **5c** and **5d**. A three-neck round bottom flask fitted with a reflux condenser and a separatory funnel was connected to argon. Mg turnings (dried under vacuum for 10 min and heated with a heating gun) and 10 mL of dry ether were added. Funnel was charged with the corresponding bromide in 35 mL of dry ether, and approximately 2 mL of this solution was added to the reaction flask with vigorous stirring. The mixture is heated with the heating gun to star the reaction. When the reaction started (small bubbles were observed), the heated was stopped and the bromide (from the

funnel) was added dropwise over 1 h under vigorous stirring. When all the bromide was added, the reaction mixture was heated under reflux (50 ºC) for 2 h. After the reaction mixture was cooled to room temperature, it was transferred with a cannula to a flask containing the aldehyde to continue with the General procedure for the synthesis of 7-(phenylsulfonyl)dec-5-en-9-yn-2-one without further purification.

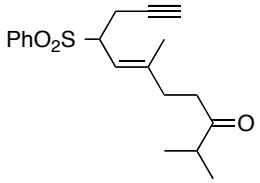
General procedure 3: Synthesis of 7-(phenylsulfonyl)dec-5-en-9-yn-2-one. A solution of the corresponding Grignard reagent (1.5 equiv) was added dropwise (30 min) to a solution of 4-methyl-6-(phenylsulfonyl)non-4-en-8-ynal in THF (0.1 M) at 0 ºC. The resulting mixture was allowed to reach ambient temperature and was stirred for 14 h. (Monitored by TLC). After quenching with aqueous saturated solution of NH_4Cl, the aqueous phase was extracted with ether, and the combined organic layers were washed with brine and dried over $MgSO_4$ prior to concentration. To a solution of the resulting alcohol in CH_2Cl_2 was added $NaHCO_3$ (5 equiv) and then Dess-Martin Periodinane (1.1 equiv) at 0 ºC. The reaction mixture was stirred for 3-10 hours and saturated aqueous $Na_2S_2O_3$ was slowly added to the mixture. After diluting with CH_2Cl_2, the mixture was extracted with 1:1 saturated aqueous $Na_2S_2O_3/H_2O$.The aqueous layer was extracted with CH_2Cl_2, and the combined organic phases were washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give the corresponding ketones.

(*E*)-5-Methyl-7-(phenylsulfonyl)dec-5-en-9-yn-2-one (5b)



Oxo-1,5-enyne **5b** was synthesized following general procedure 3, starting from (*E*)-4-methyl-6-(phenylsulfonyl)non-4-en-8-ynal **5a** (2.0 g, 6.96 mmol). The residue was purified by column chromatography (3:1 cyclohexane/EtOAc) to yield compound **5b** (1.4 g, 74%) as a yellow solid: mp 53 – 55 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.82 (m, 1.0 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.56 – 7.52 (m, 2 H), 5.06 (dd, *J* = 10.3, 1.2 Hz, 1H), 3.95 (td, *J* = 10.2, 3.8 Hz, 1H), 2.99 (ddd, *J* = 16.7, 3.5, 2.9 Hz, 1H), 2.61 (ddd, *J* = 16.7, 10.1, 2.6 Hz, 1H), 2.48 (dd, *J* = 8.6, 6.6 Hz, 2H), 2.27 (t, *J* = 7.8 Hz, 2H), 2.15 (s, 3H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.31 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.58 (C), 145.43 (C), 137.36 (C), 133.93 (CH), 129.25 (CH), 129.05 (CH), 116.17 (CH), 79.00 (C), 71.02 (CH), 62.99 (CH), 41.52 (CH_2), 33.25 (CH_2), 30.05 (CH_3), 18.82 (CH_2), 16.86 (CH_3); IR (thin film) ν 3295 (CH terminal alkyne), 1704 (C=O) cm^{-1}; HRMS-ESI *m/z* calculated for $C_{17}H_{20}O_3SNa$ $[M+Na]^+$ 327.1031, found 327.1030.

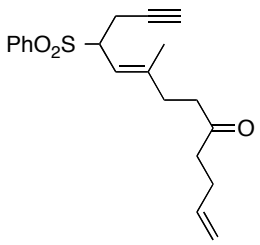
(*E*)-2,6-Dimethyl-8-(phenylsulfonyl)undec-6-en-10-yn-3-one (5c)



Oxo-1,5-enyne **5c** was synthesized generating the Grignard reagent in situ, following general procedures 2 and 3, starting from (*E*)-4-methyl-6-(phenylsulfonyl)non-4-en-8-ynal **5a** (341 mg, 1.17 mmol). The residue was purified by column chromatography (8:1 cyclohexane/EtOAc) to yield

compound **5c** (156 mg, 46%) as a yellow sticky solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.67 (m, 2H), 7.67 – 7.57 (m, 1H), 7.60 – 7.44 (m, 2H), 5.03 (dd, J = 10.3, 1.3 Hz, 1H), 3.93 (td, J = 10.2, 3.8 Hz, 1H), 2.96 (ddd, J = 16.7, 3.8, 2.7 Hz, 1H), 2.67 – 2.51 (m, 2H), 2.46 (dd, J = 8.7, 6.5 Hz, 2H), 2.22 (t, J = 7.7 Hz, 2H), 1.93 (t, J = 2.7 Hz, 1H), 1.28 (d, J = 1.3 Hz, 3H), 1.08 (s, 3H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.36 (C), 145.80 (C), 137.41 (C), 133.91 (CH), 129.29 (CH), 129.02 (CH), 115.99 (CH), 70.98 (CH), 63.04 (CH), 41.00 (CH), 38.24 (CH_2), 33.21 (CH_2), 18.83 (CH_2), 18.34 (CH_3), 16.94 ($2CH_3$); IR (thin film) ν 3272 (CH terminal alkyne), 1707 (C=O) cm^{-1}; HRMS-ESI *m/z* calculated for $C_{19}H_{24}O_3SNa$ $[M+Na]^+$ 355.1344, found 355.1329.

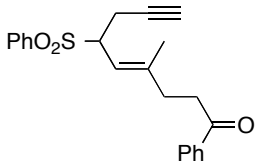
(*E*)-8-Methyl-10-(phenylsulfonyl)trideca-1,8-dien-12-yn-5-one (5d)



Oxo-1,5-enyne **5d** was synthesized generating the Grignard reagent in situ, following general procedures 2 and 3, starting from (*E*)-4-methyl-6-(phenylsulfonyl)non-4-en-8-ynal **5a** (2.55 g, 8.81 mmol). The residue was purified by column chromatography (8:1 cyclohexane/EtOAc) to yield compound **5d** (1.01 g, 33%) as a light yellow solid: mp 50 – 54 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.77 (m, 2H), 7.72 – 7.60 (m, 1H), 7.53 (tt, J = 6.8, 1.3 Hz, 2H), 5.89 – 5.66 (m, 1H), 5.07 – 4.90 (m, 3H), 3.94 (td, J = 10.2, 3.8 Hz, 1H), 2.96 (ddd, J = 16.7, 3.8, 2.7 Hz, 1H), 2.59 (ddd, J = 16.7, 10.1, 2.7 Hz, 1H), 2.55 – 2.39 (m, 4H), 2.38 – 2.16 (m, 4H), 1.93 (dd, J = 3.6, 1.8 Hz, 1H), 1.29 (d, J = 1.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.93 (C), 145.57 (C), 137.41 (C), 137.08 (CH), 133.95 (CH), 129.30

(CH), 129.07 (CH), 116.16 (CH), 115.45 (CH), 79.05 (C), 71.02 (CH), 63.05 (CH), 42.00 (CH_2), 40.76 (CH_2), 33.21 (CH_2), 27.81 (CH_2), 18.87 (CH_2), 16.94 (CH_3); IR (thin film) ν 3276 (CH terminal alkyne), 1710 (C=O) cm^{-1}; HRMS-ESI *m/z* calculated for $C_{22}H_{22}O_3SNa$ $[M+Na]^+$ 367.1344, found 367.1340.

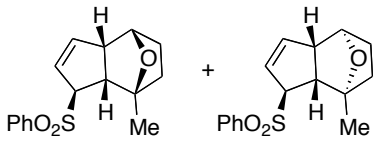
(*E*)-4-Methyl-1-phenyl-6-(phenylsulfonyl)non-4-en-8-yn-1-one (5e)



Oxo-1,5-enyne **5e** was synthesized following general procedure 3, starting from (*E*)-4-methyl-6-(phenylsulfonyl)non-4-en-8-ynal **5a** (399 mg, 1.38 mmol). The residue was purified by column chromatography (8:1 cyclohexane/EtOAc) to yield compound **5e** (312 mg, 80%) as a white solid: mp 74 – 78 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.93 (m, 2H), 7.85 – 7.83 (m, 2H), 7.63 (ddd, *J* = 6.9, 4.0, 1.2 Hz, 1H), 7.58 (ddd, *J* = 6.8, 4.0, 1.3 Hz, 1H), 7.55 – 7.45 (m, 4H), 5.13 (dd, *J* = 10.3, 1.3 Hz, 1H), 3.98 (td, *J* = 10.2, 3.8 Hz, 1H), 3.07 – 2.93 (m, 3H), 2.62 (ddd, *J* = 16.7, 10.1, 2.7 Hz, 1H), 2.44 (t, *J* = 7.5 Hz, 2H), 1.92 (t, *J* = 2.7 Hz, 1H), 1.37 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.02 (C), 145.77 (C), 137.50 (C), 136.89 (C), 133.95 (CH), 133.32 (CH), 129.38 (CH), 129.09 (CH), 128.81 (CH), 128.14 (CH), 116.45 (CH), 79.11 (C), 71.04 (CH), 63.17 (CH), 36.73 (CH_2), 33.72 (CH_2), 18.89 (CH_2), 17.10 (CH_3); IR (thin film) ν 3262 (CH terminal alkyne), 1680 (C=O) cm^{-1}; HRMS-ESI *m/z* calculated for $C_{22}H_{22}O_3SNa$ $[M+Na]^+$ 389.1187, found 389.1194.

General procedure 4: Cyclization of oxo-1,5-enynes. Oxo-1,5-enyne and the gold(I) complex (2-5 mol%) were dissolved in CH_2Cl_2 (0.5-1.2 mL) and stirred at room temperature until full conversion (TLC monitoring). One drop of Et_3N was added and the reaction crude was filtered through Celite® and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to provide the cyclized products.

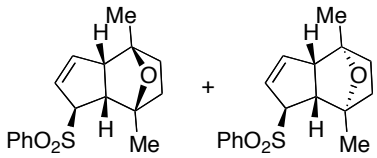
(1*R,3a*R**,4*R**,7*S*,7a*S*)-7-Methyl-1-((phenylperoxy)thio)-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-epoxyindene (6a) and (1*R**,3a*R**,4S*,7*R**,7a*S**)-7-Methyl-1-((phenylperoxy)thio)-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-epoxyindene (6a')**



Compounds **6a** and **6a'** were synthesized following general procedure 4, starting from **5a** (48.9 mg, 0.17 mmol) with catalyst **I** (5 mol%). The residue was purified by column chromatography (6:1 hexane/EtOAc) to give a 3.6:1 mixture of isomers **6a** and **6a'** (36.6 mg, 75%) as a white solid: Major isomer **6a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.85 (m, 2H), 7.75 – 7.62 (m, 1H), 7.61 – 7.51 (m, 2H), 5.99 (dt, J = 5.7, 2.0 Hz, 1H), 5.77 (dt, J = 4.3, 1.9 Hz, 1H), 4.48 (t, J = 5.6 Hz, 1H), 4.00 – 3.98 (m, 1H), 3.34 – 3.01 (m, 1H), 2.74 (dt, J = 9.5, 2.0 Hz, 1H), 1.73 – 1.51 (m, 1H), 1.51 – 1.33 (m, 2H), 1.27 – 1.25 (m, 1H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.36 (CH), 136.91 (C), 133.97 (CH), 129.49 (CH), 129.12 (CH), 125.04 (CH), 86.01 (C), 79.03 (CH), 72.35 (CH), 56.03 (CH), 52.88 (CH), 30.32 (CH_2), 28.58 (CH_2), 20.18 (CH_3); HRMS-ESI *m/z* calculated for $C_{16}H_{18}O_3SNa$ $[M+Na]^+$ 313.0874, found 313.0869. Minor isomer **6a'**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.85 (m, 2H), 7.73 – 7.60 (m, 1H), 7.63 – 7.49 (m, 2H), 5.92 (dt, J = 5.7, 2.2 Hz, 1H), 5.62 (dt, J = 5.7, 2.1 Hz, 1H),

4.26 – 4.18 (m, 1H), 4.14 (d, J = 5.1 Hz, 1H), 2.96 (ddd, J = 7.0, 4.6, 2.3 Hz, 1H), 2.72 (dd, J = 7.2, 3.1 Hz, 1H), 1.82 – 1.74 (m, 1H), 1.62 – 1.58 (m, 1H), 1.56 – 1.48 (m, 2H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.30 (CH), 137.71 (C), 133.90 (CH), 129.23 (CH), 129.17 (CH), 126.02 (CH), 84.58 (C), 78.97 (CH), 74.25 (CH), 58.21 (CH), 50.34 (CH), 36.31 (CH_2), 30.75 (CH_2), 17.99 (CH_3); HRMS-ESI *m/z* calculated for $C_{16}H_{18}O_3SNa$ $[M+Na]^+$ 313.0874, found 313.0882.

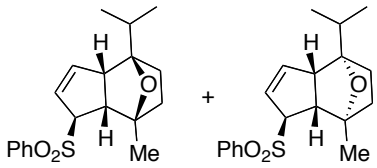
(1*R,3a*R**,4*R**,7*S**,7a*S**)-4,7-Dimethyl-1-(phenylsulfonyl)-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-epoxyindene (6b) and (1*R**,3a*R**,4*S**,7*R**,7a*S**)-4,7-dimethyl-1-(phenylsulfonyl)-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-epoxyindene (6b')**



Compounds **6b** and **6b'** were synthesized following general procedure for the cyclization of oxo-1,5-enynes, starting from **5b** (56.9 mg, 0.19 mmol) with catalyst **H** (5 mol%). The residue was purified by column chromatography (6:1 hexane/EtOAc) to give a 3.7:1 mixture of isomers **6b** and **6b'** (55.7 mg, 98%) as colourless oil: Major isomer **6b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.84 (m, 2H), 7.66 – 7.58 (m, 1H), 7.58 – 7.47 (m, 2H), 5.98 (dt, J = 5.6, 1.9 Hz, 1H), 5.75 (dt, J = 5.5, 2.0 Hz, 1H), 3.99 – 3.97 (m, 1H), 2.89 – 2.86 (m, 1H), 2.85 – 2.78 (m, 1H), 1.67 – 1.64 (m, 1H), 1.47 – 1.42 (m, 2H), 1.39 (s, 3H), 1.37 – 1.36 (m, 1H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.21 (CH), 136.95 (C), 133.91 (CH), 129.44 (CH), 129.09 (CH), 124.87 (CH), 86.35 (C), 85.60 (C), 72.98 (CH), 61.63 (CH), 53.94 (CH), 34.69 (CH_2), 31.94 (CH_2), 21.41 (CH_3), 20.42 (CH_3). Minor isomer **6b'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.84 (m, 2H), 7.66 – 7.58 (m, 1H), 7.58 – 7.47 (m, 2H), 5.91 (dt, J = 5.7, 2.2 Hz, 1H), 5.66 (dt, J = 5.7, 2.0 Hz, 1H), 4.44 – 4.09 (m, 1H), 2.90 – 2.85 (m,

1H), 2.85 – 2.74 (m, 1H), 1.59 – 1.57 (m, 1H), 1.48 – 1.38 (m, 3H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.15 (CH), 137.81 (C), 133.85 (CH), 129.19 (CH), 129.12 (CH), 126.51 (CH), 85.14 (C), 84.15 (C), 74.38 (CH), 60.58 (CH), 51.74 (CH), 38.16 (CH_2), 37.72 (CH_2), 18.31 (CH_3), 18.13 (CH_3); HRMS-ESI *m/z* calculated for $C_{17}H_{20}O_3SNa$ $[M+Na]^+$ 327.1041, found 327.1043.

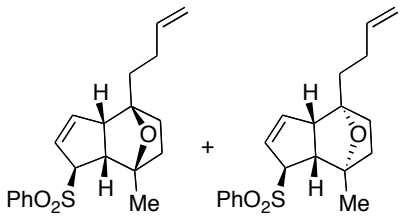
(1*R,3a*R**,4*S**,7*S**,7a*S**)-4-Isopropyl-7-methyl-1-(phenylsulfonyl)-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-epoxyindene (6c) and (1*R**,3a*R**,4*R**,7*R**,7a*S**)-4-isopropyl-7-methyl-1-(phenylsulfonyl)-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-epoxyindene (6c')**



Compounds **6c** and **6c'** were synthesized following general procedure for the cyclization of oxo-1,5-enynes, starting from **5c** (23.3 mg, 0.07 mmol) with catalyst **A** (5 mol%). The residue was purified by column chromatography (8:1 hexane/EtOAc) to give a 4:1 mixture of isomers **6c** and **6c'** (11.9 mg, 51%) as a light yellow oil: Major isomer **6c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 7.80 (m, 2H), 7.75 – 7.63 (m, 1H), 7.61 – 7.50 (m, 2H), 6.02 (dt, J = 5.6, 2.0 Hz, 1H), 5.77 – 5.70 (m, 1H), 3.96 (dt, J = 4.3, 2.2 Hz, 1H), 3.09 – 2.96 (m, 1H), 2.78 (dt, J = 9.6, 1.9 Hz, 1H), 2.02 (dt, J = 13.8, 6.9 Hz, 1H), 1.44 – 1.36 (m, 4H), 1.10 (s, 3H), 0.95 – 0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.95 (CH), 137.25 (C), 133.93 (CH), 129.37 (CH), 129.16 (CH), 124.36 (CH), 92.51 (C), 84.69 (C), 72.60 (CH), 57.98 (CH), 53.89 (CH), 33.40 (CH), 31.46 (CH_2), 30.17 (CH_2), 20.27 (CH_3), 18.13 (CH_3), 18.00 (CH_3). Minor isomer **6c'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 7.80 (m, 2H), 7.75 – 7.63 (m, 1H), 7.61 – 7.50 (m, 2H), 5.97 (dt, J = 5.8, 2.2 Hz, 1H), 5.65 (dt, J = 5.8, 2.0 Hz, 1H), 4.31 – 4.18 (m,

1H), 3.07 – 3.04 (m, 1H), 2.83 (dd, *J* = 7.3, 3.4 Hz, 1H), 1.94 – 1.85 (m, 1H), 1.70 – 1.65 (m, 2H), 1.61 – 1.50 (m, 2H), 1.28 (s, 3H), 0.95 – 0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.94 (CH), 137.25 (C), 133.86 (CH), 129.22 (CH), 129.11 (CH), 126.40 (CH), 91.44 (C), 83.74 (C), 74.51 (CH), 59.96 (CH), 51.46 (CH), 37.45 (CH_2), 30.17 (CH), 28.61 (CH_2), 18.42 (CH_3), 18.32 (CH_3), 17.12 (CH_3); HRMS-ESI *m/z* calculated for $C_{19}H_{24}O_3SNa$ $[M+Na]^+$ 355.1344, found 355.1329.

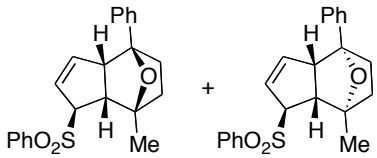
(1*R,3a*R**,4*R**,7*S**,7a*S**)-4-(But-3-en-1-yl)-7-methyl-1-(phenylsulfonyl)-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-epoxyindene (6d) and (1*R**,3a*R**,4*S**,7*R**,7a*S**)-4-(but-3-en-1-yl)-7-methyl-1-(phenylsulfonyl)-3a,4,5,6,7,7a-hexahydro-1*H*-4,7-epoxyindene (6d').**



Compounds **6d** and **6d'** were synthesized following general procedure for the cyclization of oxo-1,5-enynes, starting from **5d** (48.5 mg, 0.13 mmol) with catalyst **H** (2 mol%). The residue was purified by column chromatography (8:1 hexane/EtOAc) to give a 4:1 mixture of isomers **6d** and **6d'** (43.2 mg, 89%) as colourless oil: Major isomer **6d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.86 (m, 2H), 7.69 – 7.61 (m, 1H), 7.58 – 7.53 (m, 2H), 6.00 (dt, *J* = 5.6, 1.9 Hz, 1H), 5.84 – 5.75 (m, 1H), 5.78 – 5.72 (m, 1H), 5.11 – 4.80 (m, 2H), 3.97 (dt, *J* = 4.8, 2.2 Hz, 1H), 3.01 – 2.92 (m, 1H), 2.83 – 2.80 (m, 1H), 2.14 – 2.08 (m, 2H), 1.86 -1.81 (m, 2H), 1.55 – 1.34 (m, 4H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.79 (CH), 138.19 (CH), 137.06 (C), 133.95 (CH), 129.40 (CH), 129.13 (CH), 124.82 (CH), 114.85 (CH_2), 88.98 (C), 85.08 (C), 72.65 (CH), 60.22 (CH), 52.85 (CH), 35.10 (CH_2), 32.80 (CH_2), 31.58 (CH_2), 29.07 (CH_2), 20.28 (CH_3).

Minor isomer **6d'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.80 (m, 2H), 7.69 – 7.60 (m, 1H), 7.58 – 7.53 (m, 2H), 5.92 (dt, J = 5.7, 2.2 Hz, 1H), 5.86 – 5.80 (m, 1H), 5.66 (dt, J = 5.7, 2.0 Hz, 1H), 5.06 – 4.98 (m, 2H), 4.27 – 4.20 (m, 1H), 3.04 – 3.00 (m, 1H), 2.87 – 2.77 (m, 1H), 2.53 – 2.41 (m, 2H), 2.35 – 2.22 (m, 2H), 1.64 – 1.60 (m, 4H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.08 (CH), 137.82 (CH), 137.06 (C), 133.88 (CH), 129.22 (CH), 129.11 (CH), 126.66 (CH), 114.92 (CH_2), 87.91 (C), 83.79 (C), 74.41 (CH), 59.52 (CH), 51.39 (CH), 37.76 (CH_2), 34.73 (CH_2), 31.64 (CH_2), 29.15 (CH_2), 18.25 (CH_3); HRMS-ESI *m/z* calculated for $C_{20}H_{24}O_3SNa$ $[M+Na]^+$ 376.1344, found 367.1363.

(1*R,3a*R**,4*R**,7*S**,7a*S**)-7-Methyl-4-phenyl-1-(phenylsulfonyl)-3a,4,5,6,7,7a-hexahydro-1H-4,7-epoxyindene (6e) and (1*R**,3a*R**,4*S**,7*R**,7a*S**)-7-methyl-4-phenyl-1-(phenylsulfonyl)-3a,4,5,6,7,7a-hexahydro-1H-4,7-epoxyindene (6e')**



Compounds **6e** and **6e'** were synthesized following general procedure for the cyclization of oxo-1,5-enynes, starting from **5e** (27.4 mg, 0.08 mmol) with catalyst **H** (5 mol%). The residue was purified by column chromatography (6:1 hexane/EtOAc) to give a 4:1 mixture of isomers **6e** and **6e'** (20.8 mg, 62%) as a white solid: Major isomer **6e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.87 (m, 2H), 7.65 – 7.63 (m, 1H), 7.58 – 7.51 (m, 2H), 7.33 (d, J = 4.5 Hz, 4H), 7.29 – 7.23 (m, 1H), 6.15 (dt, J = 5.6, 2.0 Hz, 1H), 5.87 (dt, J = 4.2, 1.9 Hz, 1H), 4.24 – 3.99 (m, 1H), 3.32 – 3.10 (m, 1H), 2.96 (dt, J = 9.5, 1.9 Hz, 1H), 2.00 – 1.85 (m, 1H), 1.72 – 1.64 (m, 1H), 1.55 – 1.50 (m, 2H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.18 (C), 141.25 (CH), 136.87 (C), 134.01 (CH), 129.51 (CH), 129.15

(CH), 128.55 (CH), 127.53 (CH), 125.65 (CH), 124.98 (CH), 89.81 (C), 85.83 (C), 73.01 (CH), 63.00 (CH), 53.88 (CH), 35.19 (CH_2), 31.78 (CH_2), 20.52 (CH_3). Minor isomer **6e'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.87 (m, 2H), 7.65 – 7.63 (m, 1H), 7.58 – 7.51 (m, 2H), 7.33 (d, J = 4.5 Hz, 4H), 7.29 – 7.23 (m, 1H), 5.54 (dt, J = 5.7, 2.1 Hz, 1H), 5.35 (dt, J = 5.7, 2.2 Hz, 1H), 4.34 (dt, J = 5.1, 2.5 Hz, 1H), 3.32 (ddd, J = 7.0, 4.6, 2.4 Hz, 1H), 3.22 – 3.10 (m, 1H), 2.16 – 2.09 (m, 1H), 1.86 – 1.80 (m, 1H), 1.56 – 1.47 (m, 2H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.93 (CH), 135.68 (C), 133.89 (CH), 129.23 (CH), 129.18 (CH), 128.55 (CH), 127.17 (CH), 125.84 (CH), 125.30 (CH), 84.38 (C), 81.94 (C), 62.99 (CH), 53.87 (CH), 35.18 (CH_2), 31.78 (CH_2), 20.52 (CH_3); HRMS-ESI *m/z* calculated for $C_{22}H_{22}O_3SNa$ $[M+Na]^+$ 389.1187, found 389.1183.

Chapter 4. Gold-Catalyzed Intermolecular Cycloaddition of Furans and Alkynes

4.1. Introduction

This chapter is focused on intermolecular reactions catalyzed by gold, which have been less studied than 1,n-enynes cycloisomerizations. Among these examples, we can cite the intermolecular cycloaddition catalyzed by gold of enol ethers with *N*-allenylsulfonamides,[1] coupling of ketones, secondary amines and alkynes,[2] or intermolecular hydroamination of allenes.[3]

4.1.1. Intermolecular Gold-Catalyzed Reactions

The first gold(I)-catalyzed intermolecular reaction of alkynes with alkenes was developed in our research group, which leads to cyclobutenes using sterically hindered cationic gold(I) complexes as catalyst.[4] As it is a slow process than the mechanistically related intramolecular reactions of enynes, problems of competing olefin isomerization and/or polymerization, as well as the control of the regio- and stereoselectivity in the absence of a tether made this reaction more challenging.

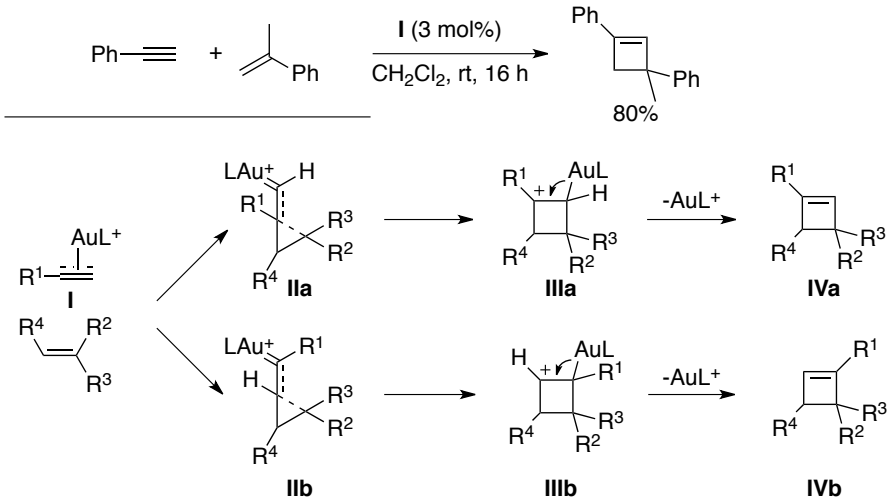
The intermolecular cycloaddition reaction proceeds via regiosiomeric cyclopropyl gold(I) carbenes **IIa**/**IIb** formed from the reaction of Au(I)-alkyne complex **I** with alkenes (***Scheme 1***).

1 Suárez-Pantiga, S.; Hernández-Díaz, C.; Piedrafita, M.; Rubio, E.; González, J. M. *Adv. Synth. Catal.* **2012**, *354*, 1651-1657.

2 Cheng, M.; Zhang, Q.; Hu, X.-Y.; Li, B.-G.; Ji, J.-X.; Chan, A. S. C. *Adv. Synth. Catal.* **2011**, *353*, 1274-1278.

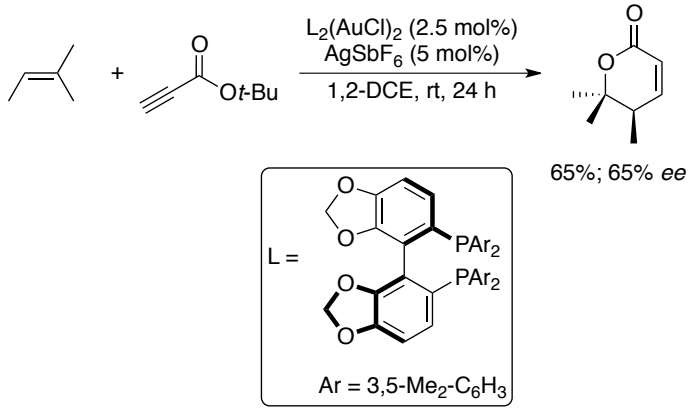
3 Wang, Z. J.; Benitez, D.; Tkatchouk, E.; Goddard IIII, W. A.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 13064-13071.

4 López-Carrillo, V.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 9292-9294.



Scheme 1. Gold(I)-catalyzed intermolecular cycloaddition of alkynes with alkenes.

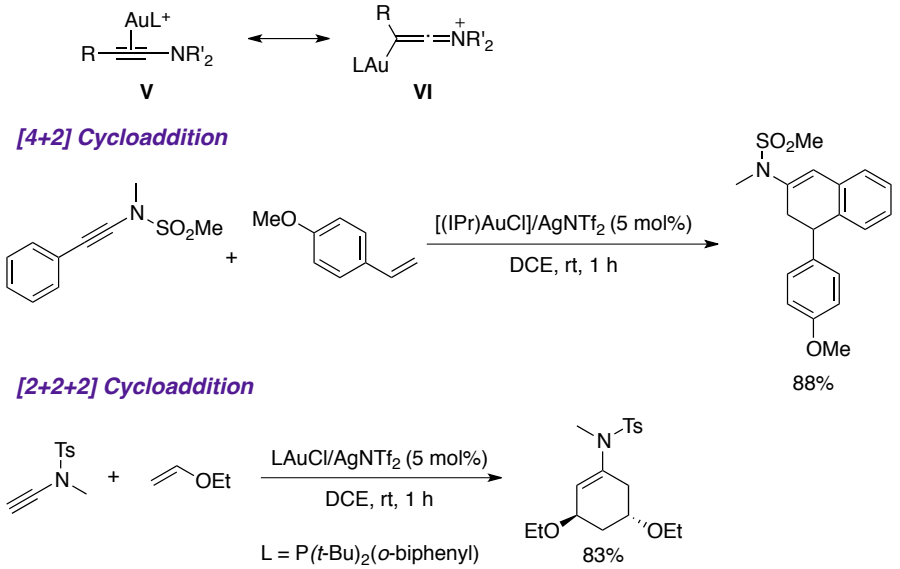
A more recent example of intermolecular transformation is the [4+2] reaction of propiolates with alkenes to form α,β-unsaturated δ-lactones (*Scheme 2*).[5] This is also the first example of an asymmetric intermolecular reaction between alkenes and alkynes via direct activation of alkynes by gold complexes.



Scheme 2. Asymmetric intermolecular reaction of alkenes and alkynes.

5 Yeom, H.-S.; Koo, J.; Park, H.-S.; Wang, Y.; Liang, Y.; Yu, Z.-X.; Shin, S. *J. Am. Chem. Soc.* **2011**, *134*, 208-211.

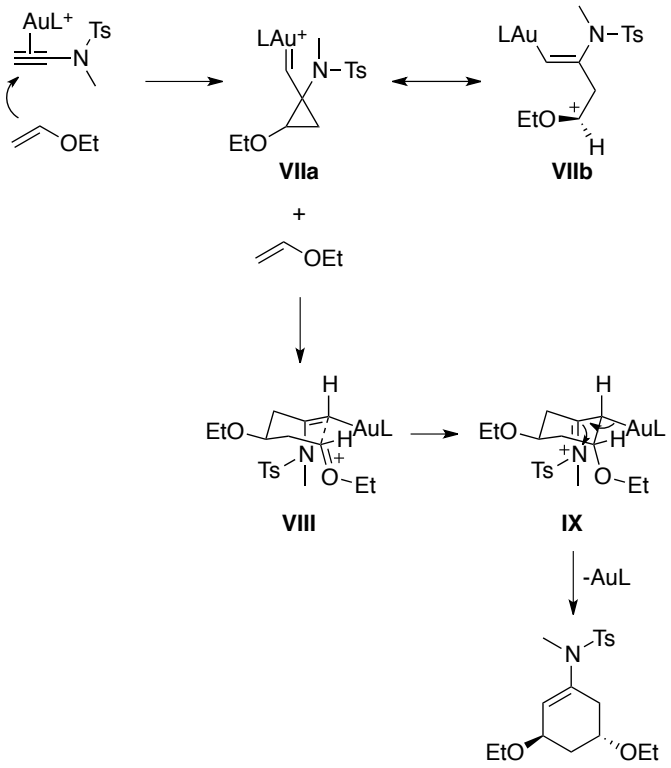
More electrophilic substrates such as ynamides have become interesting substrates for the intermolecular cycloadditions reactions.[6] The polarized π-alkyne character of the substrate-catalyst complex **V** (that can be drawn as the ketene resonance structure **VI**) affects positively the control of the regioselectivity (*Scheme 3*). Hence, good yields have been reported in the [4+2] cycloadditions of 2-arylynamides with different alkenes along with the intermolecular [2+2+2] cycloaddition of terminal ynamides with enol ethers in a highly stereoselective way (*Scheme 3*).



Scheme 3. Gold(I)-catalyzed intermolecular [4+2] and [2+2+2] cycloadditions of ynamides.

The stereoselectivity of the [2+2+2] cycloaddition was explained according to the proposed mechanism shown in *Scheme 4*.[6] The reaction proceeds via cyclopropyl gold-carbene **VIIa** with a second molecule of enol ether to form the oxonium species **VIII**, which cyclized to form **IX**. A final demetalation then forms the six-membered derivative.

6 Dateer, R. B.; Shaibu, B. S.; Liu, R.-S. *Angew. Chem. Int. Ed.* **2012**, *51*, 113-117.



Scheme 4. Proposed mechanism for the [2+2+2] cycloaddition reaction.

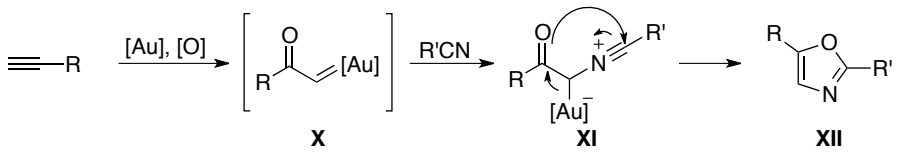
Other examples of intermolecular reactions catalyzed by gold have been also reported to get access to various heterocyclic compounds such as oxazoles,[7] furans,[8] or carbamimidates.[9] Synthesis of oxazoles is possible by either [2+2+1][7b] or [3+2][7a] intermolecular reactions. The first one involves the alkyne oxidation to generate an α-oxo gold carbene intermediate **X** which in the presence of nitriles as solvent reach rapidly enough to form intermediate **XI** avoiding side reactions (*Scheme 5*). Then, intermediate **XI** evolves via cyclization to give oxazole **XII**. This reaction proceeds under

7 (a) Davies, P. W.; Cremonesi, A.; Dumitrescu, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 8931-8935. (b) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482-8485.

8 Kramer, S.; Skrydstrup, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 4681-4684.

9 Campbell, M. J.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1369-1378.

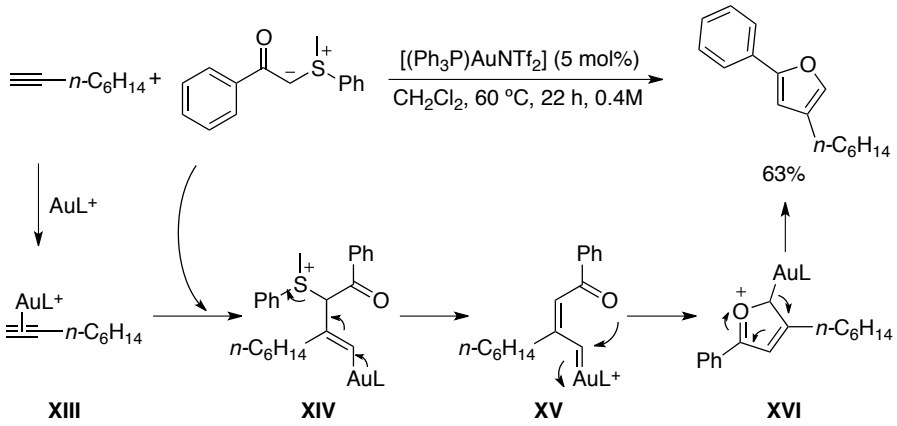
mild conditions and tolerates a variety of functional groups, avoiding the use of potentially hazardous α-diazo ketones.



Scheme 5. Gold-catalyzed alkyne oxidation: synthesis of oxazoles.

The generation of α-oxo gold carbenes from alkynes through intermolecular reaction along with an intermolecular nitrene transfer has been recently demonstrated.[7,10] In addition, the use of carbon ylides as nucleophiles to generate the gold carbene intermediate through carbene transfer to an alkyne leading to the formation of furan has been reported (*Scheme 5*).[8] The nucleophilic attack by the ylide to **XIII** is highly regioselective leading to vinyl gold intermediate **XIV**. Back donation from the gold center would lead to the liberation of the leaving group with generation of an allylic gold carbene **XV**. Trapping of **XV** by the carbonyl oxygen and metal elimination gives 2,4-substituted furans in good to high yields.

10 Li, C.; Zhang, L. *Org. Lett.* **2011**, *13*, 1738-1741.



Scheme 6. Synthesis of 2,4-disubstituted furans via intermolecular [3+2] cycloaddition.

4.1.2. Synthesis of Phenols

Phenols and its derivatives are important organic molecules due to its common uses in the industry as precursor of different materials, such as plastics, detergents, herbicides or pharmaceutical drugs.[11] Moreover, many variety of natural products contain phenolic structures.[12] Therefore, we were interested in developing a methodology that could allow accessing to phenols by an intermolecular reaction of furans with alkynes catalyzed by gold complexes. First, a brief introduction describing some examples of the synthesis of phenols using traditional synthetic methodologies and transition-metal catalysis will be described.

4.1.2.1 Synthesis of Phenols: Traditional Methodologies

The classic route to synthesize aromatic compounds is the electrophilic or nucleophilic aromatic substitution modifying an existent arene.[13] Other approaches used cycloaddition reactions such as the Diels-Alder reaction followed by oxidation of the unsaturated six-membered ring to an arene.[14]

Ring-closing olefin metathesis is one of the most elegant methodologies for the synthesis of cyclic compounds,[15] particularly for the

11 (a) Silverman, R. B., The Organic Chemistry of Drug Design and Drug Action, 2nd ed., Academic Press., **2004**. (b) Svobodova, A.; Psotova, J.; Walterova, D. *Biomed. Papers,* **2003**, *147*, 137-145. (c) Buckles, R. E.; Wawzonek, S. *J. Chem. Educ.* **1948**, *25*, 514.

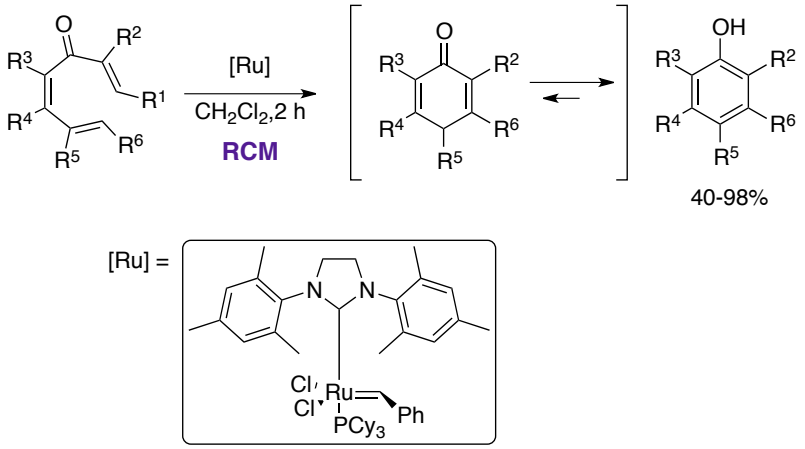
12 Manzanaro, S.; Salvá, J.; de la Fuente, J. Á. *J. Nat. Prod.* **2006**, *69*, 1485-1487.

13 (a) Hartshorn, S. R. *Chem. Soc. Rev.* **1974**, *3*, 167-192. (b) Pearson, D. E.; Buehler, C. A. *Synthesis* **1971**, 455-477.

14 Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317-361.

15 (a) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012-3043. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4450.

formation of phenols. In the last years, different approaches using ring-closing olefin metathesis from 1,4,7-trien-3-ones have been reported.[16] This is possible in part due to the tolerance that Grubbs' second generation catalyst presents to a wide range of functional groups (*Scheme 7*).

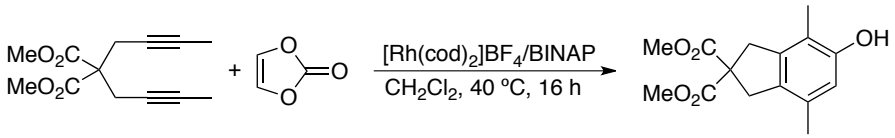


Scheme 7. Synthesis of phenol derivatives by ruthenium-catalyzed ring-closing olefin metathesis.

Recently, the synthesis of phenols was reported via [2+2+2] decarboxylative cycloadditon reaction catalyzed by cationic rhodium(I) complexes.[17] Thus, 1,6- and 1,7-diynes react with vinylene carbonate in the presence of rhodium(I) complexes to furnish substituted bicyclic phenols via elimination of carbon dioxide (*Scheme 8*).

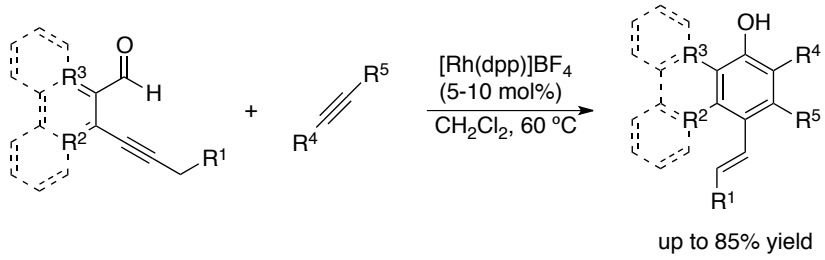
16 (a) Yoshida, K.; Imamoto, T. *J. Am. Chem. Soc.* **2005**, *127*, 10470-10471. (b) Yoshida, K.; Toyoshima, T.; Imamoto, T. *Chem. Comm.* **2007**, 3774-3776. (c)Yoshida, K.; Takahashi, H.; Imamoto, T. *Chem. Eur. J.* **2008**, *14*, 8246-8261. (d) Yoshida, K.; Narui, R.; Imamoto, T. *Chem. Eur. J.* **2008**, *14*, 9706-9713.

17 Hara, H.; Hirano, M.; Tanaka, K. *Org. Lett.* **2009**, *11*, 1337-1340.



Scheme 8. Rh(I)-catalyzed [2+2+2] cycloaddition to lead bicyclic phenols.

A new reaction catalyzed by rhodium also produced phenols, naphthols, and related derivates (*Scheme 9*).[18] This methodology consists in a cascade process involving the activation of the C-H bond of an aldehyde and [4+2] annulation followed by regeneration of the aromatic ring.

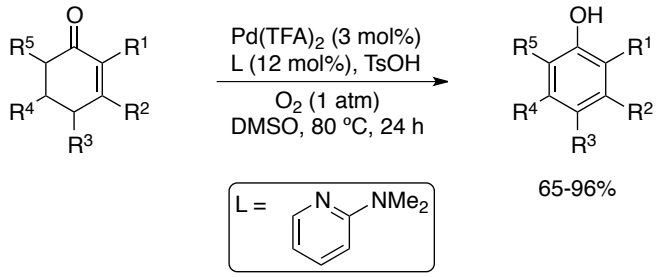


Scheme 9. Rh-catalyzed synthesis of substituted phenols and naphtols.

Phenols can also be obtained by palladium catalyzed aerobic dehydrogenation of substituted cyclohexanones.[19] The reaction proceeds via successive dehydrogenation of two saturated bonds of the cyclohexanone in the presence of molecular oxygen as hydrogen acceptor.

18 Hojo, D.; Tanaka, K. *Org. Lett.* **2012**, *14*, 1492-1495.

19 Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209-213.

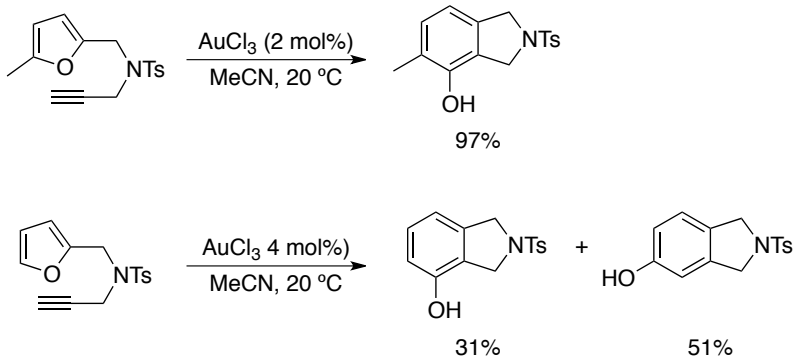


Scheme 10. Palladium-catalyzed formation of substituted phenols.

4.1.2.2 Synthesis of Phenols: Gold-Catalyzed Intramolecular Reaction

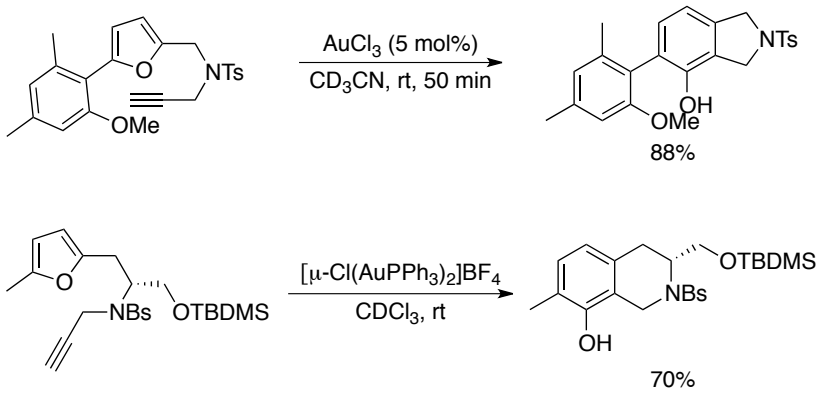
Homogeneous gold catalysis also brings the possibility of synthesize bicyclic substituted phenols in high yields. In 2000, Hashmi and co-workers reported the formation of bicyclic phenols in a highly selective gold(III)-catalyzed reaction from substituted 5-furyl-1-alkynes under mild conditions (*Scheme 11*).[20] However, the reaction is less selective with monosubstituted furans leading to a mixture of two different phenol regioisomers.

20 (a) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553-11554. (b) Hashmi, A. S. K.; Blanco, M. C.; Kurpejović, E.; Frey, W.; Bats, J. W. *Adv. Synth. Catal.* **2006**, *348*, 709-713. (c) Hashmi, A. S. K.; Ding, L.; Bats, J. W.; Fischer, P.; Frey, W. *Chem. Eur. J.* **2003**, *9*, 4339-4345. (d) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769-3771. (e) Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejović, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545-6547. (f) Hashmi, A. S. K.; Rudolph, M.; Weyrauch, J. P.; Wölfle, M.; Frey, W.; Bats, J. W. *Angew. Chem. Int. Ed.* **2005**, *44*, 2798-2801. (g) Hashmi, A. S. K.; Haufe, P.; Schmid, C.; Rivas Nass, A.; Frey, W. *Chem. Eur. J.* **2006**, *12*, 5376-5382. (h) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Chem. Eur. J.* **2006**, *12*, 6991-6996. (i) Hashmi, A. S. K.; Rudolph, M.; Siehl, H.-U.; Tanaka, M.; Bats, J. W.; Frey, W. *Chem. Eur. J.* **2008**, *14*, 3703-3708.



Scheme 11. Gold(III)-catalyzed intramolecular synthesis of phenols.

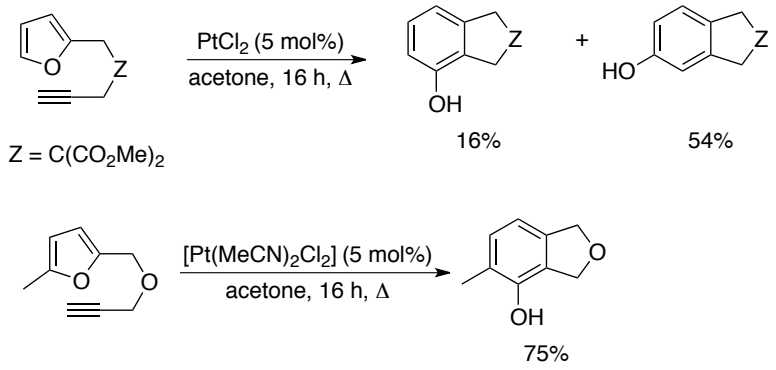
This method was successfully applied in the formation of 8-hydroxytetrahydroisoquinolines[20g] and in the synthesis of *epi*-jungianol[20c, 20h]



Scheme 12. Synthesis of dihydroisoindoles and 8-hydroxytetrahydroisoquinolines.

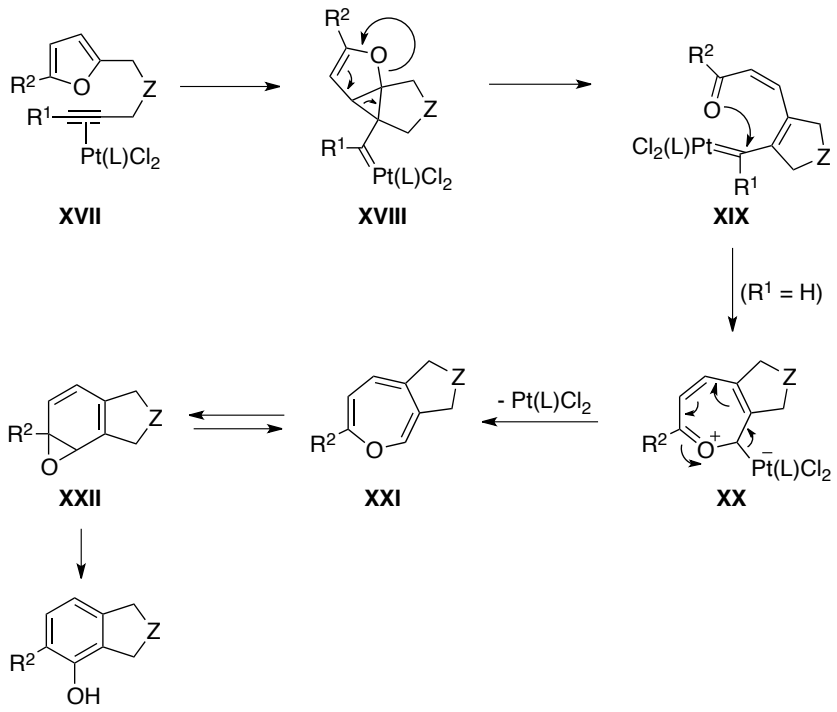
This intramolecular reaction was also achieved in good yields and selectivities using platinum(II) salts and complexes as catalysts.[21]

21 (a) Martín-Matute, B.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2001**, *40*, 4754-4757. (b) Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757-5766.



Scheme 13. Pt(II)-catalyzed intramolecular reaction of alkynes and furans.

DFT calculations carried out in our research group allowed to propose a reasonable mechanism for this transformation (*Scheme 14*).[21b] Coordination of the alkyne to the metal center forms a (η^2-alkyne)platinum(II) complex **XVII**, which triggers the nucleophilic attack of the furan leading to the formation of cyclopropyl platinum carbene **XVIII**. This step is followed by cleavage of one C-C and one C-O bonds of the tricyclic intermediate to form carbonyl compound **XIX**, which cyclizes to give **XX**. Cleavage of the C-Pt bond in **XX** generates oxepin **XXI**, which is in equilibrium with its tautomer arene oxide **XXII**. Epoxide opening in **XXII** would finally give the corresponding phenol.

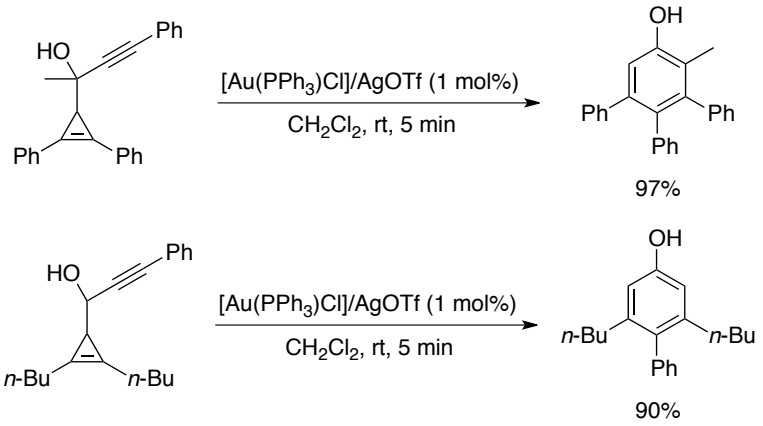


Scheme 14. Mechanism for the intramolecular reaction of furans with alkynes.

Experimental evidence for the formation of intermediates **XXI** and **XXII**[20f] were provided by the work of Hashmi's group. Furthermore, arene oxide **XXII** was trapped in a Diels-Alder reaction to form stable derivates.

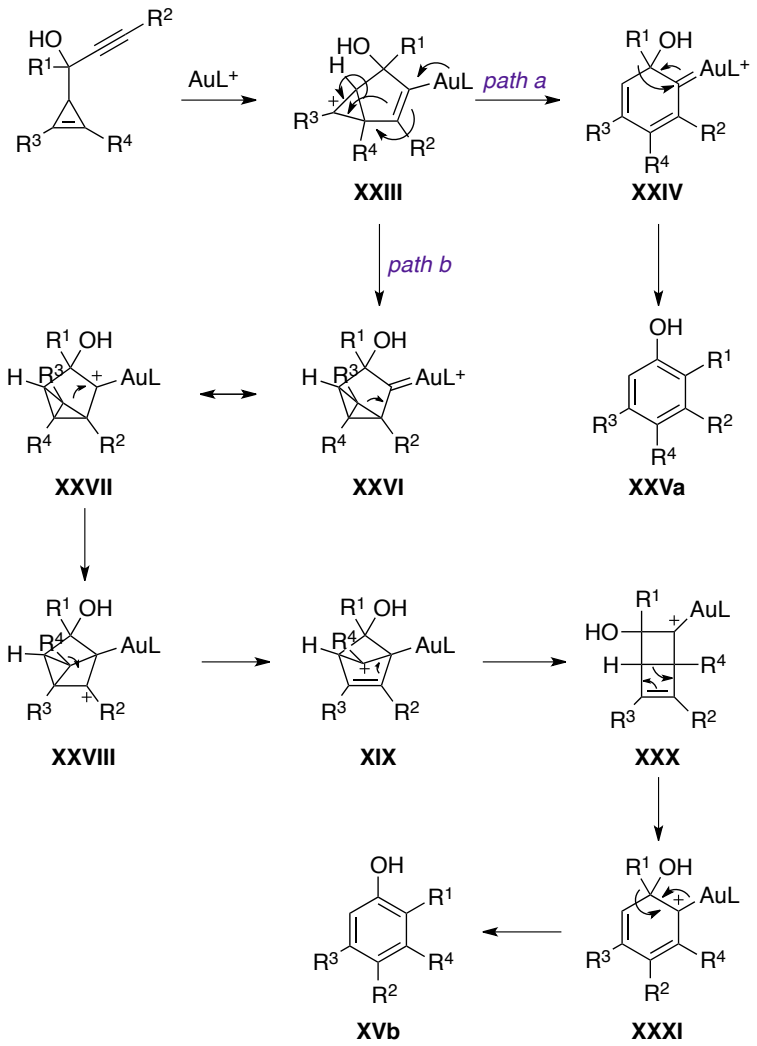
The synthesis of substituted phenols can also be achieved from gold(I)-catalyzed cycloisomerization of propargyl cyclopropenes, which can be considered formally as a 1,5-enyne system.[22]

22 Li, C.; Zeng, Y.; Zhang, H.; Feng, J.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 6413-6417.



Scheme 15. Gold(I)-catalyzed cycloisomerization of propargyl cyclopropenes.

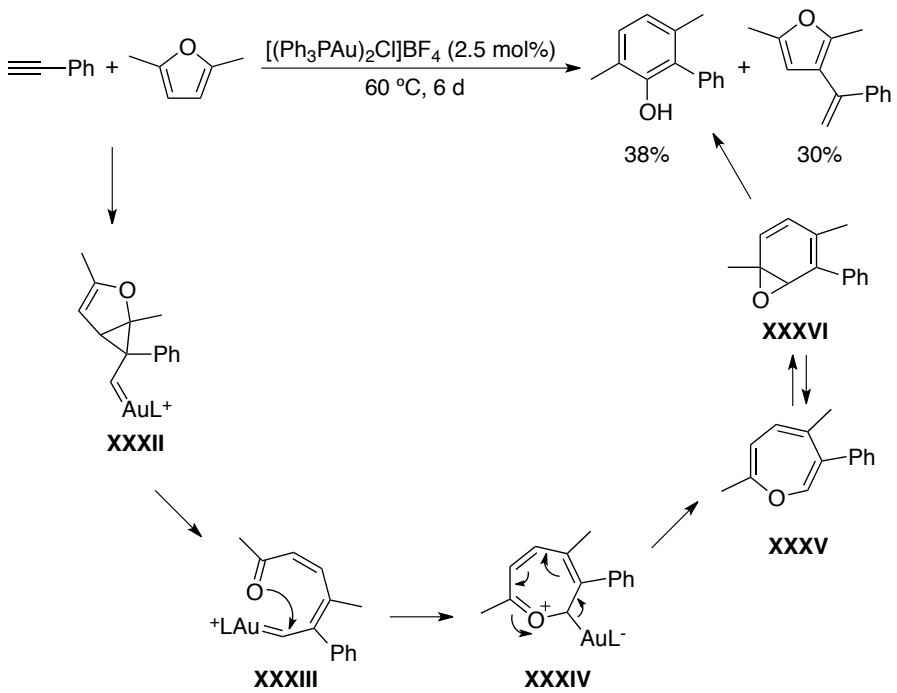
The cycloisomerization of propargyl cyclopropenes proceeds through a mechanism involving multiple alkyl migrations (*Scheme 16*). Coordination of gold to the triple bond promotes the nucleophilic attack by the cyclopropene to form bicyclo[3.1.0]hexane intermediate **XXIII** via a 5-*endo-dig* pathway. Intermediate **XXIII** could evolve via two pathways to generate different regioisomers. *Path a* leads to regioisomer **XXVa** via six-membered gold carbene **XXIV**, followed by 1,2-shift of the R^1 group. In *path b*, cyclopropyl gold(I)-carbene leads to the formation of bicyclo[1.1.0]butane intermediate **XXVI**. Then, three consecutive 1,2-alkyl shifts via carbocation species **XXVII**, **XXVIII** and **XIX** may occur to afford intermediate **XXX**. Subsequently, ring opening of **XXX** could lead to intermediate **XXXI**, which by 1,2-shift of R^1 group furnishes phenol **XVb**. In this pathway, the cleavage of both double and triple bonds are complete, whereas in *path a* no complete disconnection of double and triple bond occurs. When the substrate bears aryl groups, due to steric impediments *path a* takes place, whereas with smaller groups such as hydrogen or alkyls *path b* also occurs.



Scheme 16. Proposed mechanism for the formation of phenols from propargyl cyclopropenes.

4.2. Objectives

The gold-catalyzed intramolecular cyclization of alkynylfurans to form substituted phenols has been extensively studied.[20, 21] However, there is only one example of an intermolecular reaction of an alkyne with a furan in the presence of a binuclear gold(I) complex $[(Ph_3PAu)_2Cl]BF_4$ leading to the corresponding phenol along with the hydroarylated product.[20b, 23] This reaction requires 6 days and proceeds under relatively harsh conditions via cyclopropyl gold-carbene **XXXII** followed by the formation of oxepin **XXXV** and the arene oxide **XXXVI** intermediates, which evolves by opening of the epoxide to give the phenol in a low yield.



Scheme 17. Gold(I)-catalyzed intermolecular reaction of an alkyne with a furan.

23 Hashmi, A. S. K.; Blanco, M. C. *Eur. J. Org. Chem.* **2006**, *2006*, 4340-4342.

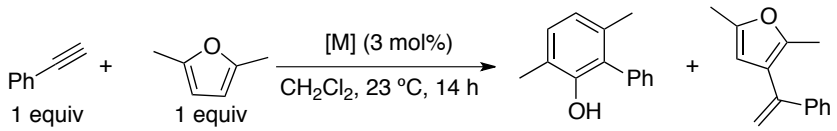
This intermolecular reaction was not selective yielding the desired phenol in 38% yield together with the hydroarylation product in 30% yield. Therefore, the objective of this work was to study this intermolecular reaction in detail using other gold(I) cationic complexes as catalysts with the goal of developing a method of general synthetic interest.

4.3. Results and Discussion

4. 3. 1 Synthesis of Phenols via Intermolecular Gold(I)-Catalyzed Reaction of Furans with Acetylenes.

Based on the result obtained by Hashmi, we focused in our first attempts on the intermolecular reaction of phenylacetylene (**1a**) with 2,5-dimethylfuran (**2**). The reaction was carried out in the presence of various catalysts (3 mol%) in CH_2Cl_2 at 23 ºC. The results are presented *Table 1*. In most of the reactions low yields of phenol **3a** were obtained or no formation of the products was observed and starting materials were recovered.

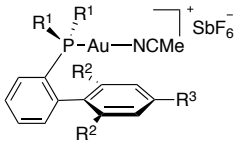
Table 1. Screening of catalyst for the synthesis of phenol **3a**.



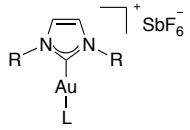
entry	[M]	product(s) (yield, %)[a]
1	**H**	**3a** (20)
2	**R**	**3a** (40)
3	**I**	**3a** (28)
4	**T**	(0)
5	**G**	**3a** (14)
6	$[Au(PPh_3)MeCN]^{+}SbF_6^{-}$	(0)
7	$[Au(PCy_3)MeCN]^{+}SbF_6^{-}$	(0)
8	$[(TolBINAP)_2Au](SbF_6)_2$	**3a** (13)
9	**U**	**3a** (4)
10	**Q**	**3a** (17)
11	**X**	**3a** (20)

12	**Y**	(0)
13	AuCl	**3a** (4)
14	$AuCl_3$	**3a** (1)
15	$AuBr_3$	(0)
16	$PdCl_2$	(0)
17	$PtCl_2$[b]	**3a** (18)
18	$PtCl_2$[c,d]	**3a** (traces)
19	$PtCl_2$[c,d]/CO	**3a** (25)
20	$PtCl_4$[d]	**3a** (36)
21	$PtCl_4$[c,d]	(c.m.)
22	**W**	**3a** (27)
23[d]	**W**	**3a** (96)
24	**Za**/$AgSbF_6$	**3a** (3) + **4a** (1)
25	**Zb**/$AgSbF_6$	**3a** (11) + **4a** (2)
26	**Zc**/$AgSbF_6$	**3a** (9)

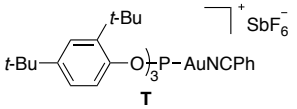
[a]Yield determined by 1,4-diacetylbenzene as internal standard. [b]0.13 equiv of catalyst. [c]Reaction carried out in toluene at 80 ºC. [d]0.10 equiv of catalyst. c.m.=complex mixture.



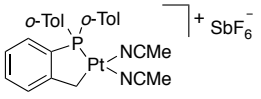
G: R^1 = Cy, R^2 = R^3 = H
H: R^1 = *t*-Bu, R^2 = R^3 = H
I: R^1 = *t*-Bu, R^2 = R^3 = *i*-Pr
J: R^1 = Cy, R^2 = OMe, R^3 = H



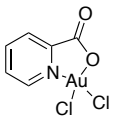
Q: R^1 = R^2 = 2,4,6-$Me_3C_6H_2$,
L = 2,4,6-$(MeO)_3C_6H_2CN$
R: R^1 = R^2 = 2,6-*i*-$Pr_2C_6H_3$,
L = PhCN
X: R^1 = Et, R^2 = Me,
L = NC-2,4,6-$(MeO)_3C_6H_2$



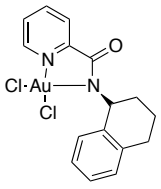
T



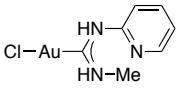
W



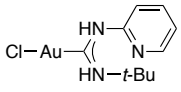
U



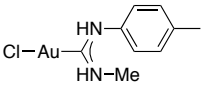
Y



Za



Zb



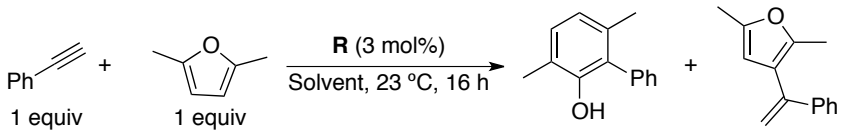
Zc

We found that in the presence of 3 mol% of NHC-gold(I) complex **R**, both starting materials **1a** and **2** were consumed to afford phenol **3a** in 40% yield (*Table 1*entry 2). Complexes with NHC ligands **Q** and **X** (*Table 1,* entries 10-11), platinum catalyst **W** (*Table 1,* entry 22), $PtCl_2$ (*Table 1,* 17) and $PtCl_4$ (*Table 1,* 20) furnished product **3a** also in moderate yields. Additionally, when 10 mol% of complex **W** were used, 96% yield of **3a** was obtained (*Table 1*, entry23). No reaction or traces of product was observed when **T**, $[Au(PPh_3)MeCN]^{+-}SbF_6$, $[Au(PCy_3)MeCN]^{+-}SbF_6$, **Y**, $AuBr_3$, or $PdCl_2$ were used as catalysts, recovering the starting materials (*Table 1*, entries 4, 6, 7, 12, 15, and 16). Using gold(III) complex **U**, AuCl, $AuCl_3$ (*Table 1*, entries 9, 13, 14), or nitrogen acyclic carbenes (NAC) such as **Za**, **Zb** and **Zc** in the presence of $AgSbF_6$, only traces of **3a** and/or **4a** were observed (*Table 1*, entries 24-26). Gold(I) catalysts bearing sterically hindered phosphine as ligand such as **G**, **H**, and **I** (*Table 1*, entries 1, 3, 5) let to the formation of phenol **3a** in moderate yields. These results are not completely surprising as we observed before in the intermolecular reaction of alkynes with alkenes,[4] increasing the steric bulkiness of the ligand on gold(I) led to a significant improvement in its selectivity.

The choice of the solvent influenced the activity of the catalytic system. Consequently, the reaction with the best cationic gold(I)-complex **R** were tested in different solvents (*Table 2*). In $CHCl_3$ or toluene, products **3a** and **4a** were obtained in low yields with a ratio close to 1:1 (*Table 2*, entries 1 and 2). Decomposition of starting materials was observed in DMSO or EtOAc (*Table 2*, entries 3 and 4), whereas in methanol, THF or DMF no reaction was observed (*Table 2*, entries 5-7). An experiment was carried out also under neat conditions giving selectively phenol **3a** in 25% yield with partial recovering of the starting materials (*Table 2*, entry 8). Additional experiments where done changing the **1a**/**2** ratio. When 2 equiv of **1a** were used (*Table 2*, entry 9), 53% of the desired phenol **3a** was obtained. Even

better result was obtained when 2 equiv of 2,5-dimethylfuran were used leading to 70% of **3a** (*Table 2*, entry 11). When the reaction was performed under microwave irradiation, a lower yield was observed due to decomposition of the starting material yielding 17% of phenol **3a** (*Table 2*, entry 12).

Table 2. Screening of solvents for the gold(I)-catalyzed intermolecular reaction of 2,5-dimethylfuran with phenylacetylene.



entry	solvent	conversion (%)	product(s) (yield, %)[a]
1	$CHCl_3$	100	**3a** (10) + **4a** (10)
2	Toluene	100	**3a** (10) + **4a** (15)
3	DMSO	0	decomposition
4	EtOAc	0	decomposition
5	MeOH	0	SM
6	THF	0	SM
7	DMF	0	SM
8	-	100	**3a** (25)
9[b]	CH_2Cl_2	100	**3a** (53)
10[b,c]	CH_2Cl_2	100	**3a** (50)
11[d]	CH_2Cl_2	100	**3a** (70)
12[e]	CH_2Cl_2	100	**3a** (17)

[a] Yield determined by 1,4-diactetylbenzene as internal standard. [b] 2 equiv of phenylacetylene were used. [c] 1 mol% of catalyst was used. [d] 2 equiv of furan were used. [e] Reaction carried out under microwave irradiation (80 ºC) for 10 min.

As platinum salts showed good to excellent activity towards the formation of phenolic product **3a** (*Table 1*, entries 17, 19-20, 22, 23), a comparison between the reactivity of gold(I)-complex **R** and platinum(II)-complex **W** was performed (*Figure 1*). A series of experiments in CH_2Cl_2 at room temperature were carried out under different catalyst loadings.[24]

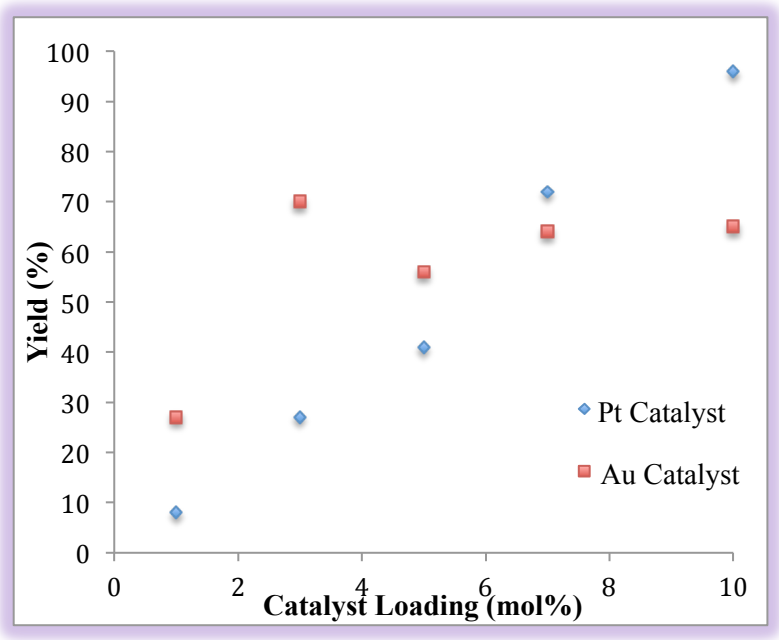
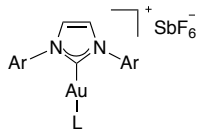
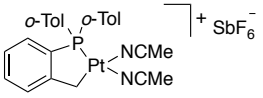


Figure 1. Comparison between Au(I)-complex **R** and Pt(II)-complex **W**.



R: Ar = 2,6-*i*-$Pr_2C_6H_3$,
L = PhCN



W

24 Study carried out in the presence of 2 equiv of furan.

Both cationic complexes **R** and **W** were active catalysts in the formation of **3a** even with low catalyst loading (*Figure 1*). Platinum complex **W** showed an almost linear tendency: the yield increased with the catalyst loading obtaining 96% yield of phenol **3a** in the presence of 0.10 equiv of **W**. However, 3 mol% of Au(I)-complex **R** gave the best result (70% yield). Higher catalyst loadings did not enhance the yield of the reaction.

Based on these different experiments, complex **R** was identified as the optimal catalyst for the formation of the phenol and compared to catalyst **W**, it is easier to prepare and requires lower catalyst loadings. Thus, we proceeded to examine the reaction scope with a wide range of acetylenes and furans in the presence of complex **R**. We first investigated the scope of aromatic and aliphatic alkynes as effective electrophiles for this reaction (*Figure 2*).

This gold(I)-catalyzed intermolecular reaction tolerates the use of phenylacetylenes bearing electron donating or electron withdrawing groups in different positions. Good yields were obtained with phenylacetylenes substituted at the ortho or para position, as is the case of phenol **3b** and **3g**. In addition, excellent yields were achieved with meta-substituted phenylacetylenes (*Figure 2*, **3c-3f**). When the reaction was carried out in the presence of 1-ethynyl-4-nitrobenzene (**1k**), 1-(4-ethynylphenyl)ethanone (**1m**), 4-ethynyl-1,2-difluorobenzene (**1o**) or 1-ethynyl-3,5-bis(trifluoromethyl)benzene (**1p**), mixture of the corresponding products **3** and **4** were observed. The reaction did not proceeded in the presence of an arylacetylene bearing amino group, and decomposition was observed (*Figure 2*, **3n**). The reaction took place satisfactorily in the presence of other alkynes such as prop-2-yn-1-ylcyclohexane and 3-ethynylthiophene leading to the corresponding phenols in moderate yields (*Figure 2*, **3s** and **3t**), but a

complex mixture was observed when (prop-2-yn-1-yloxy)benzene was used (*Figure 2*, **3z**).

The reaction also proceeds satisfactorily with aliphatic alkynes with R = cyclopropyl, *n*-hexyl, cyclohexyl and cyclohexenyl giving rise to the corresponding products **3w** (36%), **3v** (86), **3x** (50%) and **3y** (45%) in moderate to good yields respectively. However, 3,3-dimethylbut-1-yne gave no reaction probably for steric reasons.

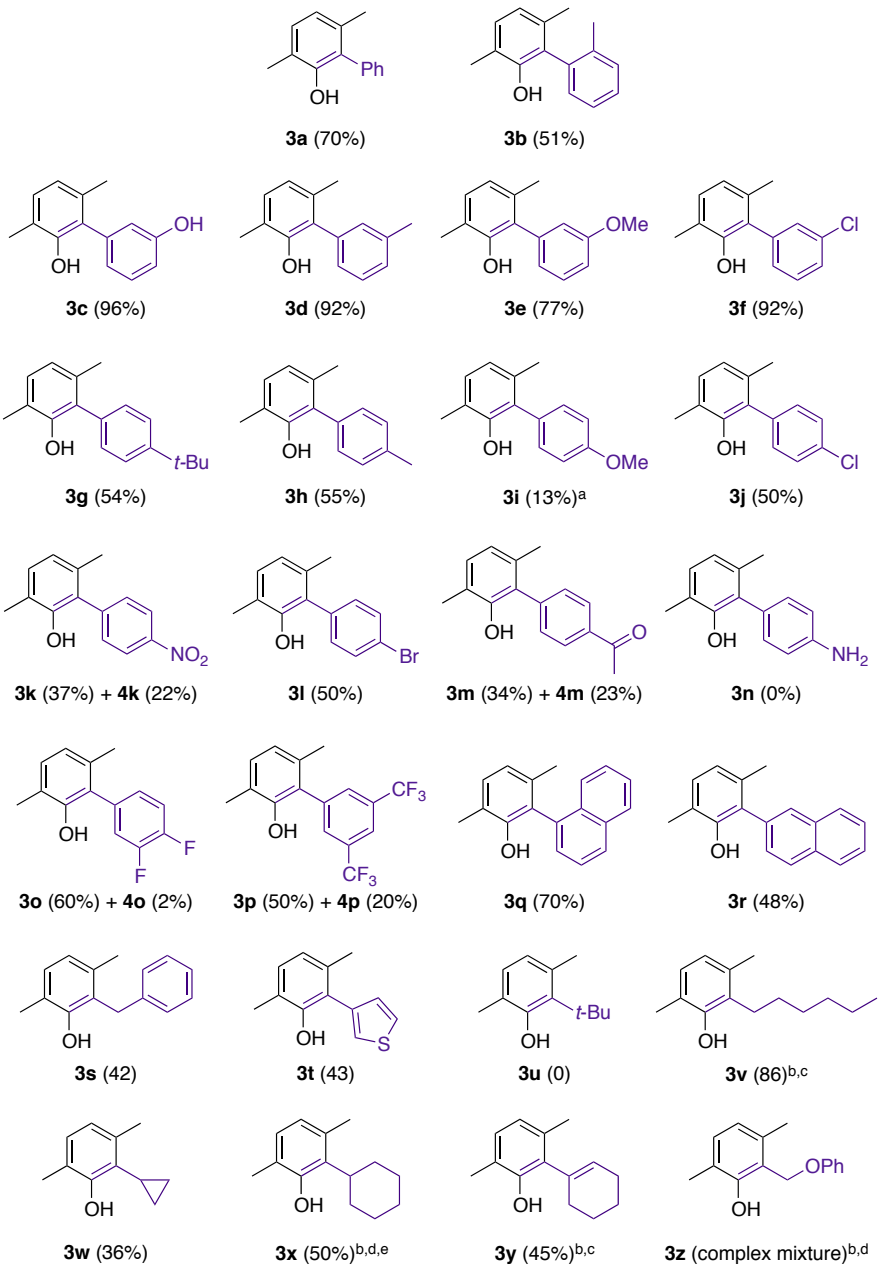
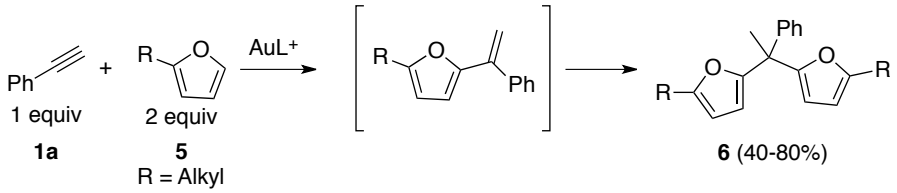


Figure 2. Study of the gold(I)-catalyzed intermolecular reaction with different acetylenes.[25]

25 Reaction carried out with 3 mol% of **R** in CH_2Cl_2, at 23 ºC for 12 h: [a] 1 equiv of furan was used. [b] Reaction carried out by Dr. David Leboeuf. [c] t =8 h. [d] t = 14 h. [e] No pure.

Next, we studied the scope of the furan substrates in the intermolecular synthesis of phenols. Not unexpected,[23] 2-alkylsubstituted furans reacted with phenylacetyne under the optimized conditions leading to the product of a twofold addition **6** in moderate to good yields (*Scheme 18*).



Scheme 18. Intermolecular gold(I)-catalyzed reaction of 2-alkylsubstituted furans and phenylacetylene.

A variety of substituted furans presented in *Figure 3* and *Figure 4* were tested under the optimum conditions in order to study the selectivity and scope of the reaction. Surprisingly, most of the reactions failed to give the desired phenols. Substituted furans such as **7a**, **7m**, **7n**, **7o**, **7p**, **7q**, **7r**, **7u**, **7v** or **7z** gave no reaction in the presence of different arylacetylenes and under different reaction conditions,[26] leading to the slow hydration of the corresponding arylacetylene with recovering of the furan. Decomposition was observed with furans bearing a TBS protected hydroxyl group (**7h** and **7l**).

26 Each furan was also tested under different conditions: gold(I) or platinum(II) catalyst, different temperatures and reaction times.

2,5-disubstituted furans

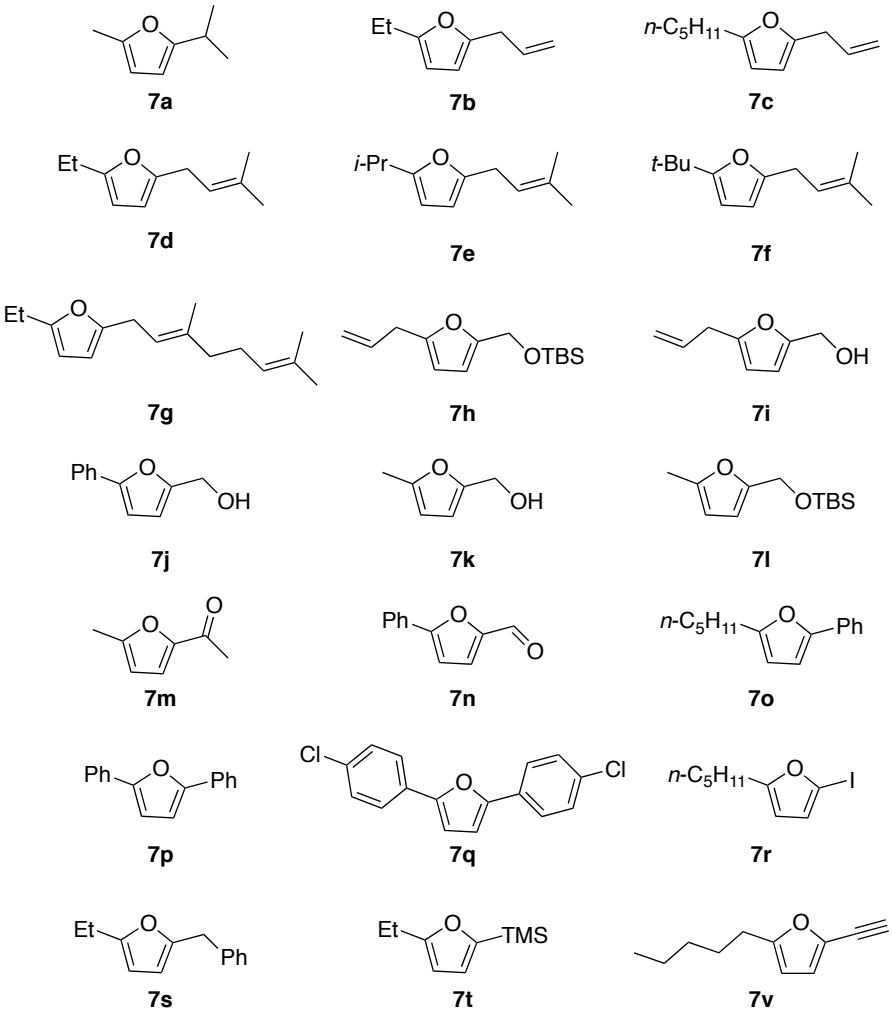


Figure 3. Scope of the reaction: tested 2,5-disubstituted furans.

other furans

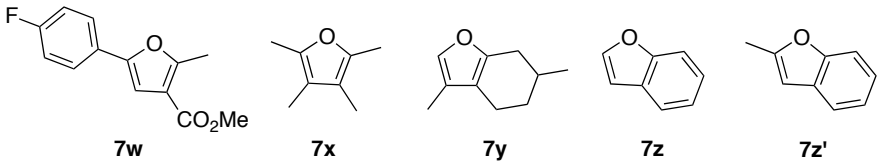
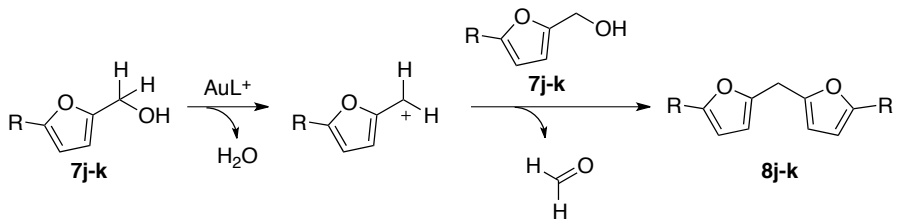
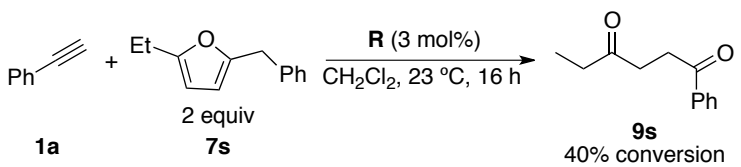


Figure 4. Scope of the reaction: other tested furans.

Unfortunately, phenol formation was not observed with furans containing a free hydroxyl group or a TMS group. Thus, furans **7j** and **7k** gave difurylmethanes **8j-k** (57% and 65% respectively) as a result of an intermolecular Friedel-Crafts-type reaction, with loss of one molecule of formaldehyde (*Scheme 19*).[27] In the case of furan **7t**, the product of twofold addition **6t** (see *Scheme 18*) was observed due to the elimination of TMS group under the reaction conditions. An additional problem was observed with furan **7s**. In this case, diketone **9s** was observed as the major product together with starting material. Product **9s** is probably formed in an acid catalyzed hydrolytic cleavage of the furan ring (*Scheme 20*).[28]



Scheme 19. Intermolecular Friedel-Crafts-type reaction. Formation of difurylmethanes **8j-k**.



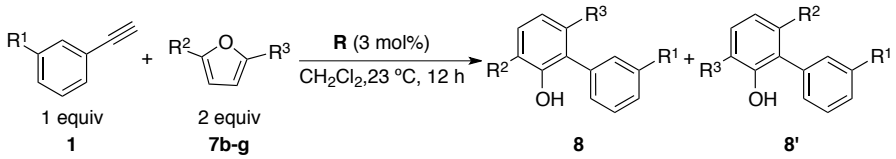
Scheme 20. Gold(I)-catalyzed intermolecular reaction of **1a** and **7s**: Formation of diketone **9s**.

27 Ji, K.-G.; Shen, Y.-W.; Shu, X.-Z.; Xiao, H.-Q.; Bian, Y.-J.; Liang, Y.-M. *Adv. Synth. Catal.* **2008**, *350*, 1275-1280.

28 Formation of the diketone product was due to the presence of traces of water in the CH_2Cl_2 obtained from the SPS system. Under neat conditions, no formation of the diketone was observed.

Finally, 2,5-disubstituted furans bearing allylic groups such as **7b-d** led to a mixture of regioisomer in phenols **8** and **8'** in moderate to excellent yields (*Table 3*, entries 1-6).

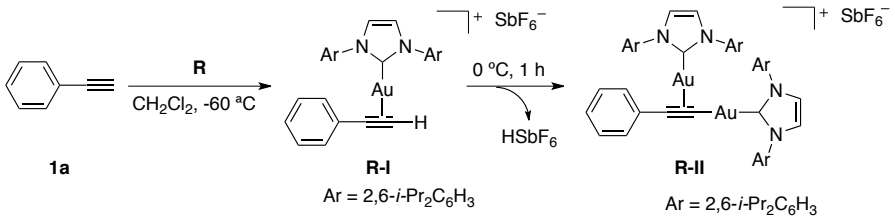
Table 3. Gold(I)-catalyzed intermolecular reaction of furans **7b-g** and arylacetylenes **1a** and **1f**: Phenols synthesis.



entry	R^1	furan	products (yield, %) ratio 3:3'
1	**1a (**H)	**7b**	**8ab + 8ab'** (39) 0.8:1
2	**1f** (Cl)	**7b**	**8fb + 8fb'** (53) 0.8:1
3	**1a** (H)	**7c**	**8ac + 8ac'** (37) 1:1
4	**1f** (Cl)	**7c**	**8fc + 8bc'** (90) 0.95:1
5	**1a (**H)	**7d**	**8ad+ 8ad'** (62) 1:1.6
6	**1f** (Cl)	**7d**	**8fd+ 8fd'** (67) 1:2
7	**1a** (H)	**7g**	SM
8	**1f** (Cl)	**7g**	SM
9	**1a** (H)	**7e**	SM
10	**1f** (Cl)	**7e**	SM
11	**1a** (H)	**7f**	SM

Surprisingly, furan **7g** bearing a geranyl group did not react under the reaction conditions and both starting materials were recovered. Similarly, when more hindered alkyl substituents, such as isopropyl or *t*-butyl groups were present in the furan, reaction was not observed (*Table 3*, entries 9-11). In the cases where the furan did not react, only hydration of the acetylene occurred in some reactions.

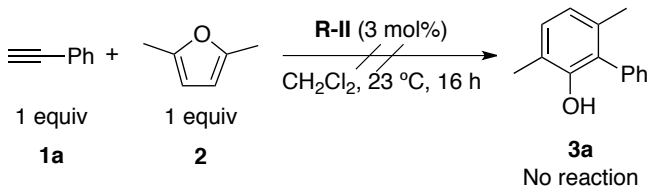
Different research groups have reported the formation of isolable digold-phenylacetylene adducts from the formation of thermally unstable gold π-alkyne complex **R-I** of the form $[(IPr)Au(\eta^2\text{-}HC{\equiv}CAr)]^+SbF_6^-$ (*Scheme 21*)[29] liberating $HSbF_6$ in the reaction media.



Scheme 21. Formation of the digold-phenylacetylene adduct **R-II**.

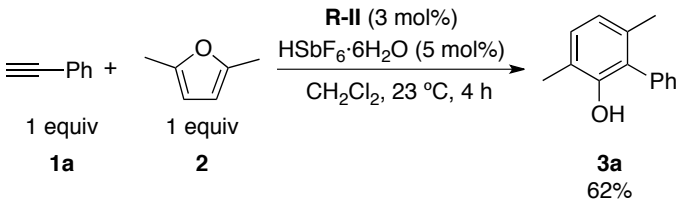
29 (a) Grirrane, A.; Garcia, H.; Corma, A.; Álvarez, E. *ACS Catalysis* **2011**, *1*, 1647-1653. (b) Brown, T. J.; Widenhoefer, R. A. *Organometallics* **2011**, *30*, 6003-6009. (c) Wei, C.; Li, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9584-9585. d) Cheong, P. H. Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 4517-4526. e) Simonneau, A.; Jaroschik, F.; Lesage, D.; Karanik, M.; Guillot, R.; Malacria, M.; Tabet, J.-C.; Goddard, J.-P.; Fensterbank, L.; Gandon, V.; Gimbert, Y. *Chem. Sci.* **2011**, *2*, 2417-2422. f) Hooper, T. N.; Green, M.; Russell, C. A. *Chem. Commun.* **2010**, *46*, 2313-2315. g) Himmelspach, A.; Finze, M.; Raub, S. *Angew. Chem.* **2011**, *123*, 2676-2679; *Angew. Chem. Int. Ed.* **2011**, *50*, 2628–2631. h) Raducan, M.; Moreno, M.; Bour, C.; Echavarren, A. M. *Chem. Commun.* **2012**, *48*, 52-54. i) Lavallo, V.; Frey, G. D.; Kousar, S.; Donnadleu, B.; Bertrand, G. *PNAS* **2007**, *104*, 13569-13573.

Cationic digold complex **R-II** was prepared according to the known procedure[29b] and was assayed as the gold catalyst in the intermolecular synthesis of phenols without success (*Scheme 22*). We therefore conclude that **R-II** is not an active catalyst for this intermolecular reaction avoiding the course of the reaction.



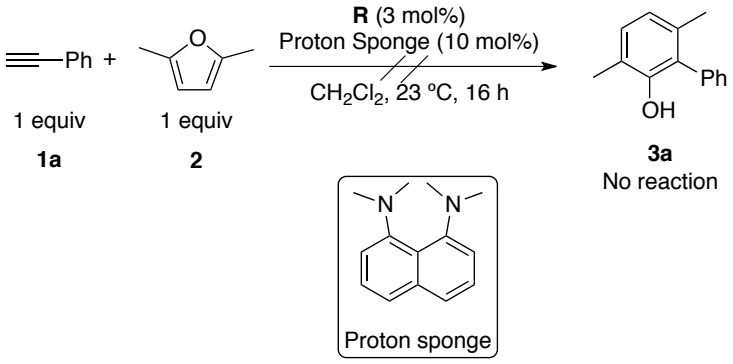
Scheme 22. Study of the reactivity of digold species **R-II**.

In an attempt to favor the formation of gold π-alkyne complex **R-I** from dinuclear gold σ,π-acetylide complex **R-II**, a slight excess of $HSbF_6$ was added to the reaction mixture. After 4 h reaction time, phenol **3a** was isolated in 62% (*Scheme 23*).



Scheme 23. Intermolecular reaction catalyzed by **R-II** in the presence of $HsbF_6$.

Liberation of $HSbF_6$ during the course of the reaction could promote the opening of the furan to the 1,4-diketone product. Thus, we tested the reaction in the presence of proton sponge.[25b] However, no reaction was observed. This result might be explained by the fact that the equilibrium between the monogold and digold species is displaced in favor of the digold complex by the trapping of $HSbF_6$ by the proton sponge, resulting in a shutdown of the reaction.

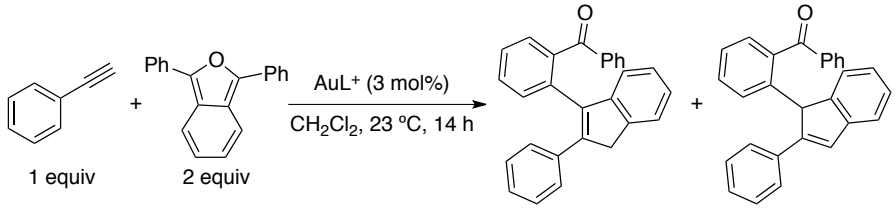


Scheme 24. Study of the intermolecular gold(I)-catalyzed synthesis of phenols in the presence of proton sponge.

4. 3. 2 Synthesis of Indenes via Intermolecular Gold(I)-Catalyzed Reaction of Furans with Acetylenes.

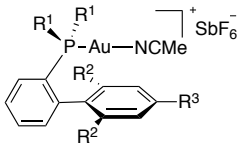
The intermolecular gold(I)-catalyzed reaction of furans with acetylenes could also be applied for the synthesis of substituted indenes. Thus, when acetylenes react with 1,3-diphenylisobenzofuran, a mixture of indenes **11** and **11'** was obtained in excellent overall yields.

Table 4. Screening of catalyst for the synthesis of indenes.

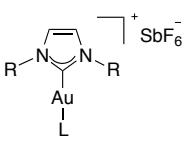


entry	AuL^+	conversion (%)	product(s) (yield, %)[a]
1	**G**	100	**11a** (46) + **11a'** (36)
2	**H**	100	**11a** (65) + **11a'** (20)
4	**Q**	-	**11a** (25)
5	**R**	100	**11a** (70) + **11a'** (23)
6	**T**	100	**11a** (72) + **11a'** (5)
7	$[Au(PPh_3)MeCN]^+SbF_6^-$	64	**11a** (3)
8	**U**	0	SM

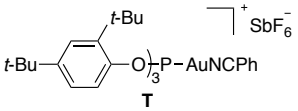
[a] Yield determined by 1,4-diactetylbenzene as internal standard.



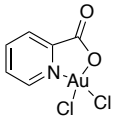
G: R^1 = Cy, R^2 = R^3 = H
H: R^1 = *t*-Bu, R^2 = R^3 = H



Q: R^1 = R^2 = 2,4,6-$Me_3C_6H_2$,
L = 2,4,6-$(MeO)_3C_6H_2CN$
R: R^1 = R^2 = 2,6-*i*-$Pr_2C_6H_3$,
L = PhCN



T



U

We were pleased to observe the formation of indenes **11a** and **11a'** with most of the gold(I) complexes tested (*Table 4*). However, when using gold(III) complex **U**, no reaction was observed (*Table 4*, entry 8). An excellent yield was obtained when NHC complex **R** was employed, and better selectivity was achieved in the presence of the most active gold(I) complex **T**. The structure of indene **11a'** was confirmed by X-ray diffraction (*Figure 5*).

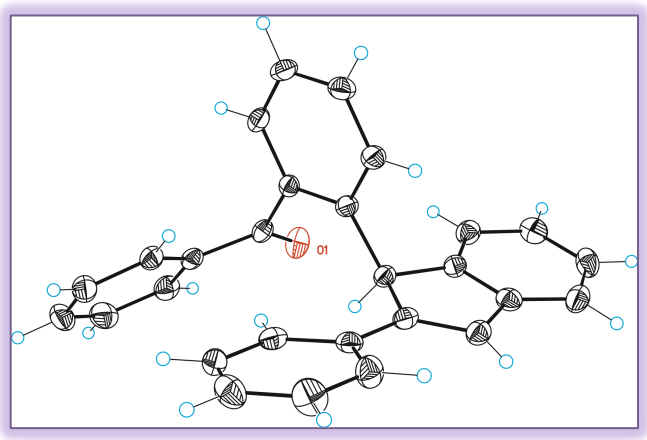
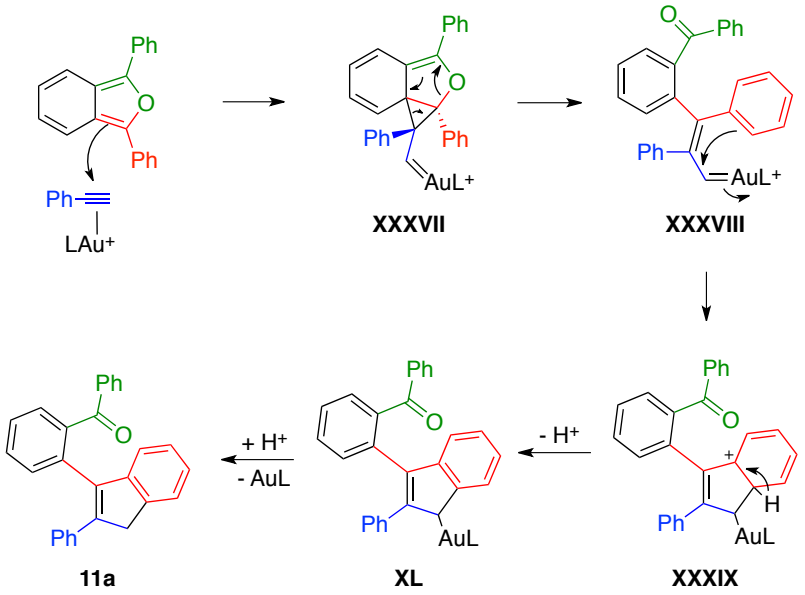


Figure 5. X-Ray structure of **11a'**.

The proposed mechanism of this reaction is similar to the intermolecular gold(I)-catalyzed reaction of furans with alkynes. Accordingly, the gold(I)-complex activates the alkynes promoting the nucleophilic attack from 1,3-diphenylisobenzofuran forming the intermediate cyclopropyl gold-carbene **XXXVII** (*Scheme 25*). Opening of **XXXVII**, followed by the attack of the aromatic ring to the gold carbene, gives intermediate **XXXIX**. Deprotonation followed by protodemetalation leads to indene **11a**, which can undergo isomerization to form regioisomer **11a'**.[30]

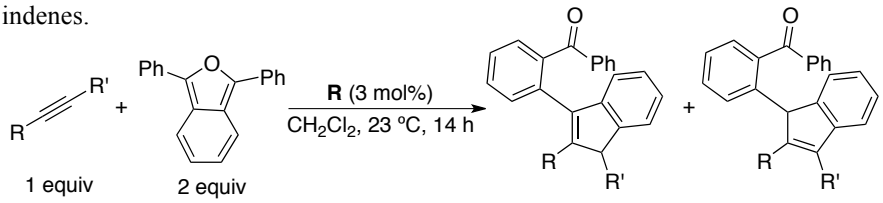
30 Isomer **11a'** is less sterically congested. Simple semiempirical calculations (PM3, Spartan 10) shows that **11a'** is 3.5 Kcal·mol^{-1} more stable than **11a**. (Spartan 10).



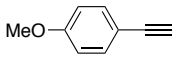
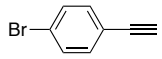
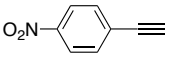
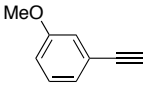
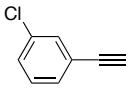
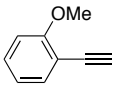
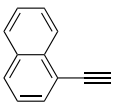
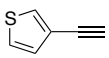
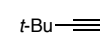
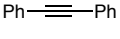
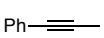
Scheme 25. Mechanim for the gold(I)-catalyzed formation of indenes.

The scope of the reaction was studied in the presence of different alkynes (*Table 5*). This reaction tolerates electron-donating and withdrawing groups in orto, meta, and para position giving rise to the corresponding indenes in high yields. When the reaction was carried out with aryl alkynes with electron donating groups such as MeO, Br, or Cl, mixtures of indenes were observed with **11** as the major product (*Table 5*, entries 2-3, 5-6). Isomeres **11** were formed as the only products in good yields when 1-ethynyl-4-nitrobenzene, 1-ethynylnaphthalene, prop-2-yn-1-ylbenzene ethynylcyclopropane, or 3-ethynylthiophene where used (*Table 5*, entries 4, 8-11 respectively). However, the reaction did not take place in the presence of 3,3-dimethylbut-1-yne (*Table 5*, entry 13) or with disubtituted alkynes (*Table 5*, entries 14-15).

Table 5. Scope of the intermolecular gold(I)-catalyzed reaction in the formation of indenes.



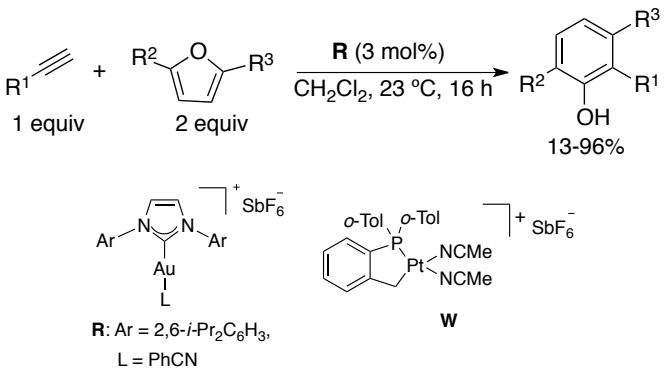
1 equiv 2 equiv **10** **11a-k** **11a-k'**

entry	alkyne	conversion (%)	product(s) (yield, %)
1		<99	**11a** (70) + **11a'** (23)
2		<99	**11b** (68) + **11b'** (32)
3		<99	**11c** (77) + **11c'** (23)
4		<99	**11d** (49)
5		<99	**11e** (82) + **11e'** (18)
6		<99	**11f** (84) + **11f'** (16)
7		<99	**11g** (85) + **11g'** (14)
8		<99	**11h** (90)
9		<99	**11i**(42)
10		<99	**11j** (96)
11		<99	**11k** (91)
12		0	-[a]
13		0	-[a]
14		0	-[a]

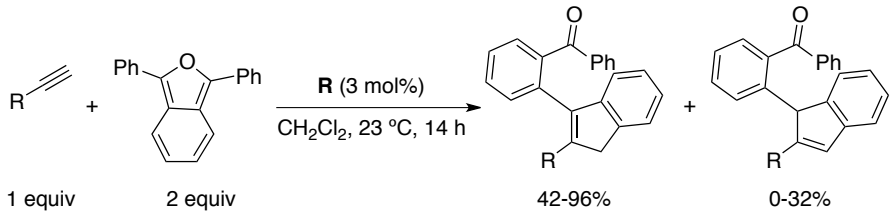
[a] No reaction.

4.4. Conclusions

The intermolecular gold(I)-catalyzed reaction between acetylenes and furans have been developed achieving the synthesis of trisubstituted phenols in good to excellent yields and improving the conditions previously reported.[23] The best results were achieved in the presence of gold(I)-complex **R** or platinum(II)-complex **W** under mild conditions.



A new methodology has been developed for the synthesis of disubstituted indenes by an intermolecular gold(I)-catalyzed reaction between terminal alkynes and 1,3-diphenylisobenzofuran. This reaction tolerates electron donating and electron withdrawing groups on the aryl alkyne and proceeds via a Friedel-Crafts type attack of the aromatic moiety to a gold(I) carbene.



4.5. Experimental Section

General Procedures

All reactions were carried out under argon in solvents dried using a Solvent Purification System (SPS). Thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck GF_{234}). Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm) or automated flash chromatographer CombiFlash Companion. NMR spectra were recorded at 23 ºC on a Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatus. Mass spectra were recorded on a Waters LCT Premier (ESI) and Waters GCT (EI, CI) spectrometers. IR spectra were performed on a FTIR Bruker Alpha apparatus. Melting points were determined using a Büchi melting point apparatus.

Complex **F**[31] was used as received from Aldrich. The following gold(I) complexes were prepared according to described procedures: **G**,[31] **I**,[31] **Q**,[32] **R**,[32] **T**,32 **W**[33] and **U**[34].

Compounds **7a**,[35] **7h**,[36] **7i**,[36] **7k**,[36, 37] **7l**,[36] **7n,**[38] **7p**,[39] and **7w**,[40] were synthesized according to literature procedures.

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

32 Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721-7730.

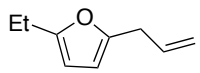
33 Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306-6316.

34 Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejović, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545-6547.

Preparation of Substrates

General procedure 1: synthesis of 2-alkyl-5-allylfurans.[36] To a solution of 2-alkylfuran (1.00 equiv.) in THF (20 mL), *n*-BuLi (1.10 equiv) was added at -10 ºC. After 4 h allyl bromide (1.10 equiv.) was added and the mixture was stirred overnight at rt. After extractive work up (Et_2O), and automated flash chromatography the title product was obtained.

2-Allyl-5-ethylfuran (7b)



Furan **7b** was synthesized following the general procedure 1, starting from 2-ethylfuran (1.10 mL, 10.09 mmol), *n*-BuLi (4.36 mL, 11.0 mmol; 2.5 M in hexanes) and allylbromide (0.96 mL, 11.0 mmol). The residue was purified by automated flash chromatography (24.0 g RediSep flash column, cyclohexane/EtOAc 22.5 min gradient 5% EtOAc) to give compound **7b** (550 mg, 40%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 – 5.96 (m, 1H), 5.96 – 5.89 (m, 2H), 5.25 – 5.06 (m, 2H), 3.39 (d, J = 6.5 Hz, 2H), 2.65 (q, J = 7.5 Hz, 2H), 1.26 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7 (C), 152.0 (C), 134.5 (CH), 116.6 (CH_2), 105.9 (CH), 104.5 (CH), 32.8 (CH_2), 21.5 (CH_2), 12.3 (CH_3); HRMS-ESI *m/z* calculated for $C_9H_{13}O$ $[M+H]^+$ 137.0966, found 137.0966.

35 Xu, J.; Caro-Diaz, E. J. E.; Batova, A.; Sullivan, S. D. E.; Theodorakis, E. A. *Chem. Asian J.* **2012**, *7*, 1052-1060.

36 Ph.D. Thesis of Belén Martín-Matute, **2002**.

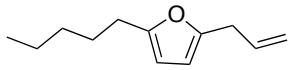
37 Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1995**, *117*, 1954-1964.

38 Bussolari, J. C.; Rehborn, D. C. *Org. Lett.*, **1999**, *1*, 965-967.

39 Surya Prakash Rao, H.; Jothilingam, S. *J. Org. Chem.* **2003**, *68*, 5392-5394.

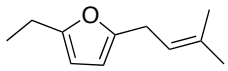
40 He, C.; Guo, S.; Ke, J.; Hao, J.; Xu, H.; Chen, C.; Lei, A. *J. Am. Chem. Soc.*, **2012**, *134*, 5766– 5769.

2-Allyl-5-pentylfuran (7c)



Furan **7c** was synthesized following the general procedure 1, starting from 2-pentylfuran (1.13 mL, 7.02 mmol), *n*-BuLi (3.03 mL, 7.65 mmol; 2.5 M in hexanes) and allylbromide (0.67 mL, 7.65 mmol). The residue was purified by automated flash chromatography (24 g RediSep flash column, cyclohexane/EtOAc 22 min gradient 5% EtOAc) to give compound **7c** (909 mg, 73%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 – 5.65 (m, 3H), 5.20 – 4.95 (m, 2H), 3.34 (d, J = 6.4 Hz, 2H), 2.56 (t, J = 7.6 Hz, 2H), 1.69 – 1.53 (m, 2H), 1.32 (td, J = 7.1, 5.8, 3.4 Hz, 4H), 1.04 – 0.83 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5 (C), 151.9 (C), 134.5 (CH), 116.6 (CH_2), 105.9 (CH), 105.2 (CH), 32.8 (CH_2), 31.6 (CH_2), 28.0 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 14.14 (CH_3); HRMS-ESI *m/z* calculated for $C_{12}H_{19}O$ $[M+H]^+$ 179.1436, found 179.1436.

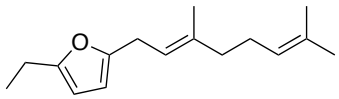
2-Ethyl-5-(3-methylbut-2-en-1-yl)furan (7d)



Furan **7d** was synthesized following the general procedure 1, starting from 2-ethylfuran (1.09 mL, 10.3 mmol), *n*-BuLi (7.08 mL, 11.3 mmol; 1.6 M in hexanes) and prenylbromide (1.31 mL, 11.3 mmol). The residue was purified by automated flash chromatography (24 g RediSep flash column, cyclohexane/EtOAc 13.3 min gradient 5% EtOAc) to give compound **7d** (1.41 g, 84%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (d, J = 1.1 Hz, 2H), 5.35 (dddd, J = 7.1, 5.7, 2.9, 1.4 Hz, 1H), 3.33 (d, J = 7.3 Hz, 2H), 2.64 (qd, J = 7.6, 1.6 Hz, 2H), 1.78 (s, 3H), 1.71 (s, 3H), 1.24 (tq, J = 7.5, 1.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 156.6 (C), 153.8 (C), 134.0

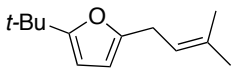
(C) 120.22 (CH), 105.4 (CH), 104.7 (CH), 27.6 (CH_3), 26.1 (CH_3), 21.8 (CH_2), 18.2 (CH_2), 12.6 (CH_3).

(*E*)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-5-ethylfuran (7g)



Furan **7g** was synthesized following the general procedure 1, starting from 2-ethylfuran (1.10 mL, 10.1 mmol), *n*-BuLi (4.36 mL, 11.0 mmol) and geranyl bromide (2.18 mL, 11.0 mmol). The residue was purified by automated flash chromatography (24 g RediSep flash column, cyclohexane/EtOAc 22 min gradient 5% EtOAc) to give compound **7g** (2.17 g, 93%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (s, 2H), 5.37 (ddd, J = 9.9, 5.0, 3.5 Hz, 1H), 5.22 – 5.09 (m, 1H), 3.34 (d, J = 7.2 Hz, 2H), 2.64 (q, J = 7.6 Hz, 2H), 2.12 (qd, J = 7.7, 3.6 Hz, 4H), 1.72 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H), 1.25 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3 (C), 153.5 (C), 137.4 (C), 131.6 (C), 124.4 (CH), 119.7 (CH), 105.1 (CH), 104.4 (CH), 39.8 (CH_2), 27.2 (CH_2), 26.7 (CH_2),25.9 (CH_3), 21.5 (CH_2), 17.8 (CH_3), 16.2 (CH_3), 12.4 (CH_3); HRMS-ESI *m/z* calculated for $C_{16}H_{25}O$ $[M+H]^+$ 233.1905, found 233.1901.

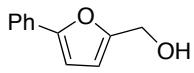
2-(*tert*-Butyl)-5-(3-methylbut-2-en-1-yl)furan (7f)



Furan **7f** was synthesized following the general procedure 1, starting from 2-*tert*-butylfuran (1.15 mL, 18.05 mmol), *t*-BuLi (5.12 mL, 8.70 mmol) and prenyl bromide (1.01 mL, 8.78 mmol) at -78 ºC. The residue was purified by automated flash chromatography (40 g RediSep flash column, cyclohexane/EtOAc 16 min gradient 5% EtOAc) to give compound **7f** (1.06 g, 69%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 – 5.69 (m, 2H),

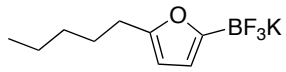
5.34 (t, J = 7.2 Hz, 1H), 3.32 (dq, J = 7.6, 1.2 Hz, 2H), 1.77 (d, J = 1.6 Hz, 3H), 1.71 (d, J = 1.5 Hz, 3H), 1.28 (q, J = 0.8 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (C), 153.3 (C), 133.8 (C), 119.8 (CH), 104.7 (CH), 102.3 (CH), 32.7 (C), 29.3 (CH_3), 27.3 (CH_2), 25.8 (CH_3), 17.9 (CH_3).

5-Phenyl-2-furanemethanol (7j)



To a stirred suspension of $LiAlH_4$ (0.22 g, 5.81 mmol) in Et_2O (10 mL) at 0°C a solution of 5-phenylfurfural (**7n**) (1.00 g, 5.81 mmol) was added. The mixture was stirred at this temperature for 1 h. The reaction was quenched cautiously with a 1.0 M Rochelle´s salt solution and stirred for additional 5 h. The mixture was extracted with EtOAc and dried over $MgSO_4$. After evaporation of the solvent the title compound was obtained as a white solid (498 mg, 99%): mp 62-64°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, J = 8.4, 1.2 Hz, 2H), 7.38-7.33 (m, 2H), 7.27-7.21 (m, 1H), 6.58 (d, J = 3.2 Hz, 1H), 6.36 (d, J = 3.2 Hz, 1H), 4.65 (br s, 2H), 1.77 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 153.98 (C), 153.45 (C), 130.56 (C), 128.59 (CH), 127.42 (CH), 123.73 (CH), 109.95 (CH), 105.63 (CH), 57.63 (CH_2).

Potassium Trifluoro(5-pentylfuran-yl)borate (7o')[41]

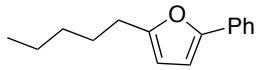


To a solution of 2-pentylfuran in DME (20 mL), *n*-BuLi (3.18 mL, 7,96 mmol; 2.5 M in hexanes) was added at -10 ºC and the reaction was stirred for 4 hours. The mixture was further cooled to -40 ºC and trimethylborate (949 mg, 9.04 mmol) was added dropwise and DME (20 mL) and the

[41] US2004/127731 A1 p.30

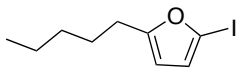
mixture was stirred overnight. It was cooled to 0 ºC and potassium hydrogen fluoride (2.79 g, 36.2 mmol) was added in one portion. It was followed by the dropwise addition of H_2O (20 mL), then the ice bath was removed and the mixture was stirred for 30 min, then concentrated under high vacuum. The solid was washed with CH_2Cl_2 to remove organic impurities. Then, the solid was dissolved in hot acetone and evaporated under vacuum to yield the product **7o'** (600 mg, 34%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.60 (s, 1H), 2.41 (t, J = 7.7 Hz, 2H), 1.92 (p, J = 2.2 Hz, 2H), 1.22 - 1.17 (m, 4H), 0.88 – 0.68 (m, 3H); HRMS-ESI *m/z* calculated for $C_9H_{14}OF310B$ $[M\text{-}K]^-$ 204.1048, found 204.1040.

2-Pentyl-5-phenylfuran (7o)



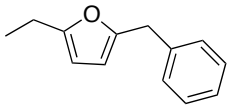
A mixture of potassium trifluoro(5-pentylfuran-yl)borate **7o'** (287 mg, 1.18 mmol), iodo benzene (110 μL, 0.98 mmol), $Pd(Ac)_2$ (11.0 mg, 0.05 mmol), triphenylphosphine (64.3 mg, 0.25 mmol), and potassium carbonate (271 mg, 1.96 mmol) in MeOH (5 mL) was stirred at 60 ºC in a microwave flask for 24 hours. The mixture was evaporated in high vacuum and purified by automated flash chromatography (12 g RediSep flash column, cyclohexane/EtOAc 21 min gradient 5% EtOAc) to yield **7o** (157 mg, 75%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.53 (m, 2H), 7.40 – 7.28 (m, 2H), 7.25 – 7.09 (m, 1H), 6.53 (d, J = 3.2 Hz, 1H), 6.04 (dd, J = 3.2, 1.0 Hz, 1H), 2.82 – 2.52 (m, 2H), 1.96 – 1.57 (m, 2H), 1.36 – 1.34 (m, 4H), 1.03 – 0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5 (C), 152.1 (C), 131.3 (C), 128.6 (CH), 126.7 (CH), 123.6 (CH), 106.9 (CH), 105.7 (CH), 31.5 (CH_2), 28.2 (CH_2), 27.9 (CH_2), 22.5 (CH_2), 14.1 (CH_3); HRMS-ESI *m/z* calculated for $C_{15}H_{19}O$ $[M+H]^+$ 215.1436, found 215.1434.

2-Iodo-5-pentylfuran (7r)



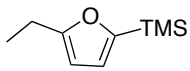
Furan **7r** was synthesized following the general procedure 1, starting from 2-pentylfuran (1.13 mL, 7.02 mmol), *n*-BuLi (3.09 mL, 7.72 mmol) and 1,2-diiodoethane (2.20 g, 7.72 mmol). The residue was purified by automated flash chromatography (40 g RediSep flash column, cyclohexane/EtOAc 17 min gradient 5% EtOAc) to give compound **7r** (1.7 g, 93%) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (d, J = 3.2 Hz, 1H), 5.90 (d, J = 3.1 Hz, 1H), 2.62 (t, J = 7.7 Hz, 2H), 1.64 – 1.58 (m, 2H), 1.32 – 1.30 (qt, J = 5.2, 2.6 Hz, 4H), 1.04 – 0.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (C), 120.7 (CH), 108.1 (CH), 84.3 (C), 31.4 (CH_2), 28.3 (CH_2), 27.8 (CH_2), 22.5 (CH_2), 14.1 (CH_3); HRMS-ESI *m/z* calculated for $C_9H_{14}OI$ $[M+H]^+$ 265.0089, found 265.0092.

2-Benzyl-5-ethylfuran (7s)



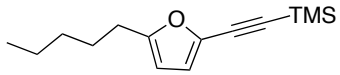
Furan **7s** was synthesized following the general procedure 1, starting from 2-ethylfuran (1.10 mL, 10.1 mmol), *n*-BuLi (4.53 mL, 11.3 mmol) and benzyl bromide (1.35 mL, 11.3 mmol). The residue was purified by automated flash chromatography (12 g RediSep flash column, cyclohexane/EtOAc 21 min gradient 5% EtOAc) to give compound **7s** (1.9 g, 99%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.06 (m, 5H), 5.86 (t, J = 2.4 Hz, 2H), 3.91 (t, J = 2.3 Hz, 2H), 2.61 - 2.57 (m, 2H), 1.21 - 1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.1 (C), 128.9 (C), 128.9 (C), 128.8 (CH), 128.5 (CH), 126.5 (CH), 106.8 (CH), 104.5 (CH), 21.5 (CH_2), 12.3 (CH_3); HRMS-ESI *m/z* calculated for $C_{13}H_{15}O$ $[M+H]^+$ 187.1123, found 187.1122.

(5-Ethylfuran-2-yl)trimethylsilane (7t)



Furan **7t** was synthesized following the general procedure 1, starting from 2-ethylfuran (1.09 mL, 10.3 mmol), *n*-BuLi (7.08 mL, 11.3 mmol, 1.6 M in hexanes) and chlorotrimethylsilane (1.44 mL, 11.3 mmol). The residue was purified by automated flash chromatography (24 g RediSep flash column, cyclohexane/EtOAc 17 min gradient 5% EtOAc) to give compound **7t** (1.4 g, 82%) as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (t, J = 2.4 Hz, 1H), 6.01 (q, J = 2.1 Hz, 1H), 2.72 (q, J = 7.5 Hz, 2H), 1.28 (td, J = 7.6, 1.9 Hz, 3H), 0.29 (d, J = 1.7 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4 (C), 158.3 (C), 120.5 (CH), 104.1 (CH), 21.7 (CH_2), 12.3 (CH_3), -1.4 (CH_3).

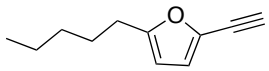
Trimethyl((5-pentylfuran-2-yl)ethynyl)silane (7u')



To a solution of 2-iodo-5-pentylfuran **7r** (209 mg, 0.79 mmol) in a mixture of degassed Et_3N and DIPA (1:1, 2 mL) were added at rt sequentially $Pd(PPh_3)_2Cl_2$ (27.9 mg, 0.04 mmol), CuI (15.1 mg, 0.08 mmol), and ethynyltrimethylsilane (159 mg, 1.59 mmol). The mixture was stirred for 12 hours. To the reaction was added a saturated solution of NH_4Cl and the resulting mixture was extracted with DCM. The combined organic phases were washed with a saturated solution of NaCl and dried over Na_2SO_4. The mixture was evaporated in high vacuum and purified by automated flash chromatography (12 g RediSep flash column, cyclohexane/EtOAc 29 min gradient 5% EtOAc) to yield **7u'** (165 mg, 88%) as a orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (d, J = 3.3 Hz, 1H), 5.95 (dt, J = 3.3, 0.9 Hz, 1H), 2.87 – 2.50 (m, 2H), 1.63 (ddt, J = 8.5, 7.3, 6.2 Hz, 2H), 1.32 – 1.30 (m, 4H), 1.01 – 0.76 (m, 2H), 0.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3 (C), 135.3 (C), 117.0 (CH), 106.2 (CH), 99.0 (C), 94.9 (C), 31.5

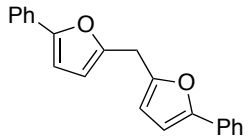
(CH_2), 28.4 (CH_2), 27.7 (CH_2), 22.5 (CH_2), 14.1 (CH_3), -0.1 (CH_3); HRMS-ESI *m/z* calculated for $C_{14}H_{23}OSi$ $[M+H]^+$ 235.1518, found 235.1515.

2-Ethynyl-5-pentylfuran (7u)



To a solution of trimethyl((5-pentylfuran-2-yl)ethynyl)silane **7u'** in THF (2 mL), tetrabutylammonium fluoride (0.35 mL, 0.35 mmol) was added and stirred for 1 h. The crude mixture was extracted with diethyl ether, washed with a saturated solution of NaCl, dried over MgSO4, and evaporated under high vacuum. Purification by automated flash chromatography (4 g RediSep flash column, cyclohexane/EtOAc 14 min gradient 5% EtOAc) to yield **7u** (164.6, 88%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, J = 3.3 Hz, 1H), 6.10 – 5.79 (m, 1H), 3.39 (s, 1H), 2.97 – 2.52 (m, 2H), 1.66 – 1.62 (m, 2H), 1.38 – 1.26 (m, 4H), 1.04 – 0.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (C), 132.4 (C), 117.3 (CH), 106.1 (CH), 81.5 (CH), 74.6 (C), 31.4 (CH_2), 28.4 (CH_2), 27.7 (CH_2), 22.5 (CH_2), 14.1 (CH_3).

Bis(5-phenylfuran-2-yl)methane (8j)

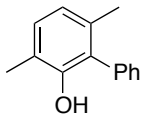


A mixture of (5-phenylfuran-2-yl)methanol **7j** (100 mg, 0.57 mmol), formic acid (0.09 mL, 2.30 mmol), sulfuric acid (0.92 μL, 0.02 mmol), and Pd/C (48.9 mg, 0.05 mmol) was stirred at 100 ºC for 1 hour under microwave conditions. The crude product was purified by automated flash chromatography (4 g RediSep flash column, cyclohexane/EtOAc 14 min gradient 5% EtOAc) to yield bis(5-phenylfuran-2-yl)methane (64.0 g, 37

%) as a yellow oil. The spectroscopic data were identical to those reported.[42]

General procedure 2: synthesis of phenols. A solution of the corresponding acetylene (1 equiv) and the substituted furane (2 equiv) in dry CH_2Cl_2 (0.2 mL) was added to a solution of gold(I) catalyst (3 mol%) in dry CH_2Cl_2 (0.2 mL). The mixture changes from yellow, green and blue consecutively. The reaction was stirred at room temperature for 14 h (brown mixture). Then, a drop of triethylamine was added (orange solution), the solvent was removed under vacuum and the crude was purified by column chromatography to give the corresponding phenol.

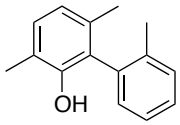
3,6-Dimethyl-[1,1'-biphenyl]-2-ol (3a)



Phenol **3a** was synthesized following the general procedure 2, starting from phenylacetylene (0,02 mL, 0.18 mmol) and 2,5-dimethylfuran (0,04 mL, 0.36 mmol). The residue was purified by column chromatography (40:1 cyclohexane/EtOAc) to give compound **3a** (22 mg, 60%) as an orange oil. The spectroscopic data were identical to those reported.[20b]

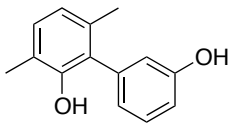
42 Characterization described on: Ke-Gong, J.; Yong-Wen, S.; Xing-Zhong, S.; Hui-Quan, H.; Yong-Jiang, B.; Yong-Min, L. *Advanced Synthesis and Catalysis*, **2008** , *350*, 1275 – 1280.

2',3,6-Trimethyl-[1,1'-biphenyl]-2-ol (3b)



Phenol **3b** was synthesized following the general procedure 2, starting from 1-ethynyl-2-methylbenzene (36.9 mg, 0.31 mmol) and 2,5-dimethylfuran (59.8 mg, 0.62 mmol). The residue was purified by column chromatography (40:1 cyclohexane/EtOAc) to give compound **3b** (33.1 mg, 51%) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.28 (m, 3H), 7.16 (dd, J = 6.8, 1.9 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 4.53 (s, 1H), 2.26 (s, 3H), 2.07 (s, 3H), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.7 (C), 138.1 (C), 134.8 (C), 134.5 (C), 131.0 (CH), 130.7 (CH), 129.8 (CH), 128.7 (CH), 126.9 (CH), 126.9 (C), 121.4 (CH), 121.3 (C), 19.9 (CH_3), 19.6 (CH_3), 16.0 (CH_3); IR (thin film) ν 3545.0, 3504.3, 2947.5, 1460.4, 1159.4, 1003.1, 736.9 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{15}H_{15}O$ [*M*-H]$^-$ 211.1123, found 211.1131.

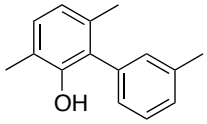
3,6-Dimethyl-[1,1'-biphenyl]-2,3'-diol (3c)



Phenol **3c** was synthesized following the general procedure 2, starting from 3-ethynylphenol (21.7 mg, 0.18 mmol) and 2,5-dimethylfuran (35.6 mg, 0.37 mmol). The residue was purified by column chromatography (20:1 DCM/MeOH) to give compound **3c** (37.9 mg, 96%) as a light yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 8.1, 7.6 Hz, 1H), 7.12 – 6.96 (m, 1H), 6.91 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 6.87 (dt, J = 7.5, 1.2 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.75 (dd, J = 2.7, 1.5 Hz, 1H), 5.39 (s, 1H), 4.92 (s, 1H), 2.28 (s, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.5 (C), 150.8 (C), 137.4 (C), 134.4 (C), 131.0 (CH), 129.9 (CH), 127.3 (C), 122.7 (CH), 121.6 (C), 121.5 (CH), 117.2 (CH), 115.3 (CH), 20.2 (CH_3),

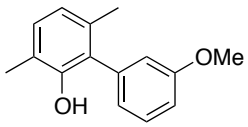
16.1 (CH_3); IR (thin film) ν 3545.6, 3492.1, 2951.9, 1592.1, 1379.4, 1177.58, 1158.2, 1076.2, 784.5, 701.9 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{14}H_{13}O_2$ [*M*-H]$^-$ 213.0916, found 213.0911.

3,3',6-Trimethyl-[1,1'-biphenyl]-2-ol (3d)



Phenol **3d** was synthesized following the general procedure 2, starting from 1-ethynyl-3-methylbenzene (18.0 mg, 0.15 mmol) and 2,5-dimethylfuran (29.2 mg, 0.30 mmol). The residue was purified by column chromatography (40:1 cyclohexane/EtOAc) to give compound **3d** (29.3 mg, 92%) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.5 Hz, 1H), 7.31 – 7.18 (m, 1H), 7.20 – 7.09 (m, 2H), 7.06 (d, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 4.84 (s, 1H), 2.44 (s, 3H), 2.29 (s, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.9 (C), 139.3 (C), 135.7 (C), 134.4 (C), 130.9 (CH), 129.8 (CH), 129.5 (CH), 128.9 (CH), 127.8 (C), 127.4 (CH), 121.5 (C), 121.4 (CH), 21.6 (CH_3), 20.3 (CH_3), 16.1 (CH_3); IR (thin film) ν 3548.6, 2922.1, 1460.6, 1190.1, 802.2, 781.1, 706.1 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{15}H_{15}O$ [*M*-H]$^-$ 211.1123, found 211.1131.

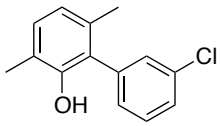
3'-Methoxy-3,6-dimethyl-[1,1'-biphenyl]-2-ol (3e)



Phenol **3e** was synthesized following the general procedure, starting from 1-ethynyl-3-methoxybenzene (20.8 mg, 0.15 mmol) and 2,5-dimethylfuran (29.3 mg, 0.30 mmol). The residue was purified by column chromatography (40:1 cyclohexane/EtOAc) to give compound **3e** (26.5 mg, 77%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 8.3, 7.5 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.97 (ddd, *J* = 8.4, 2.6, 1.0 Hz, 1H), 6.87 (dt, *J* =

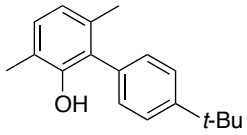
7.4, 1.2 Hz, 1H), 6.83 (dd, *J* = 2.7, 1.5 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 4.85 (s, 1H), 3.84 (s, 1H), 2.26 (s, 1H), 2.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.6 (C), 150.9 (C), 137.2 (C), 134.5 (C), 130.8 (CH), 129.9 (CH), 127.6 (C), 122.5 (CH), 121.6 (C), 121.5 (CH), 115.6 (CH), 114.1 (C), 55.5 (CH_3), 20.3 (CH_3), 16.1 (CH_3); IR (thin film) ν 3436.5, 2925.6, 1586.7, 1464.4, 1420.2, 1226,8, 1204.7, 1178.6, 1037.7, 802.7, 789.4, 700.7 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{15}H_{15}O_2$ [*M*-H]$^-$ 227.1072, found 227.1076.

3'-Chloro-3,6-dimethyl-[1,1'-biphenyl]-2-ol (3f)



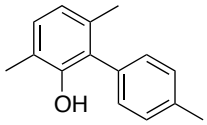
Phenol **3f** was synthesized following the general procedure, starting from 1-chloro-3-ethynylbenzene (22.2 mg, 0.16 mmol) and 2,5-dimethylfuran (30.6 mg, 0.32 mmol). The residue was purified by column chromatography (40:1 cyclohexane/EtOAc) to give compound **3f** (33.6 mg, 92%) as a orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.38 (m, 2H), 7.33 (d, *J* = 1.9 Hz, 1H), 7.20 (dt, *J* = 6.9, 1.7 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 4.66 (s, 1H), 2.27 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.8 (C), 137.9 (C), 135.4 (C), 134.5 (C), 130.8 (CH), 130.6 (CH), 130.3 (CH), 128.7 (CH), 128.5 (CH), 126.5 (C), 121.8 (C), 121.7 (CH), 20.3 (CH_3), 16.0 (CH_3); IR (thin film) ν 3563.9, 2922.7, 1594.4, 1594.4, 1562.1, 1493.7, 1160.4, 1075.4, 804.9, 697.6 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{14}H_{12}OCl$ [*M*-H]$^-$ 231.0577, found 231.0587.

4'-(*tert*-Butyl)-3,6-dimethyl-[1,1'-biphenyl]-2-ol (3g)



Phenol **3g** was synthesized following the general procedure 2, starting from 1-(*tert*-butyl)-4-ethynylbenzene (30.7 mg, 0.19 mmol) and 2,5-dimethylfuran (18.1 mg, 0.19 mmol). The residue was purified by column chromatography (40:1 cyclohexane/EtOAc) to give compound **3g** (25.7 mg, 54%) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.3 Hz, 1H), 7.33 – 7.17 (m, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 4.87 (s, 1H), 2.27 (s, 2H), 2.06 (s, 2H), 1.40 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.2 (C), 151.1 (C), 134.7 (C), 132.5 (C), 130.1 (CH), 129.7 (CH), 127.6 (C), 126.5 (CH), 121.5 (C), 121.4 (CH), 34.9 (C), 31.5 (CH_3), 20.42 (CH_3), 16.1 (CH_3); IR (thin film) ν 3547.5, 2964.2, 1416.1, 908.0, 828.4, 733.1 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{18}H_{21}O$ [*M*-H]$^-$ 253.1592, found 253.1601.

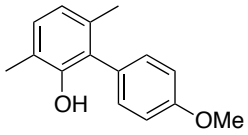
3,4',6-Trimethyl-[1,1'-biphenyl]-2-ol (3h)



Phenol **3h** was synthesized following the general procedure 2, starting from 1-ethynyl-4-methylbenzene (36,6 mg, 0.31 mmol) and 2,5-dimethylfuran (59.4 mg, 0.61 mmol). The residue was purified by column chromatography (40:1 cyclohexane/EtOAc) to give compound **3h** (35.7 mg, 55%) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.22 – 7.14 (m, 2H), 7.03 (d, J = 7.6 Hz, 1H), 6.76 (d, J = 7.6 Hz, 1H), 4.81 (s, 1H), 2.43 (s, 3H), 2.26 (s, 3H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.1 (C), 138.1 (C), 134.6 (C), 132.6 (C), 130.3 (CH), 130.3 (CH), 129.7 (CH), 127.6 (C), 121.5 (C), 121.4 (CH), 21.4 (CH_3), 20.3 (CH_3), 16.1 (CH_3); IR (thin film) ν 3547.2, 2921.4, 1490.8, 1207.3, 1090.5, 816.9,

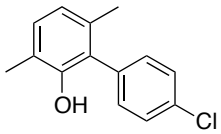
798.5, 494.9 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{15}H_{15}O$ $[M\text{-}H]^-$ 211.1123, found 211.1130.

4'-Methoxy-3,6-dimethyl-[1,1'-biphenyl]-2-ol (3i)



Phenol **3i** was synthesized following the general procedure 2, starting from 1-ethynyl-4-methoxybenzene (25.3 mg, 0.19 mmol) and 2,5-dimethylfuran (18.1 mg, 0.19 mmol). The residue was purified by column chromatography (40:1 cyclohexane/EtOAc) to give compound **3i** (5.6 mg, 13%) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 2H), 7.08 – 6.99 (m, 3H), 6.75 (d, J = 7.6 Hz, 1H), 4.81 (d, J = 0.6 Hz, 1H), 3.87 (s, 3H), 2.25 (s, 3H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4 (C), 151.1 (C), 134.8 (C), 131.5 (CH), 129.6 (CH), 127.4 (C), 127.2 (C), 121.3 (C), 121.2 (CH), 114.9 (CH), 55.3 (CH_3), 20.2 (CH_3), 16.0 (CH_3); IR (thin film) ν 3445.2, 2921.7, 2850.9, 1029.7, 1013.7, 797.5 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{15}H_{15}O_2$ $[M\text{-}H]^-$ 227.1072, found 227.1075.

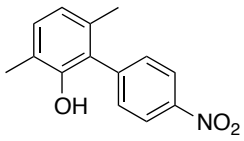
4'-Chloro-3,6-dimethyl-[1,1'-biphenyl]-2-ol (3j)



Phenol **3j** was synthesized following the general procedure 2, starting from 1-chloro-4-ethynylbenzene (30.0 mg, 0.22 mmol) and 2,5-dimethylfuran (42.7 mg, 0.44 mmol). The residue was purified by column chromatography (40:1 cyclohexane/EtOAc) to give compound **3j** (24.0 mg, 50%) as yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.25 – 7.18 (m, 2H), 7.10 – 6.99 (dd, J = 7.7, 0.8 Hz, 1H), 6.76 (d, J = 7.7 Hz, 1H), 4.61 (s, 1H), 2.24 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.9 (C),

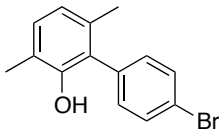
134.5 (C), 134.3 (C), 131.9 (CH), 130.2 (C), 129.8 (CH), 129.8 (CH), 126.5 (C), 121.7 (C), 121.7 (CH), 20.3 (CH_3), 16.1 (CH_3); IR (thin film) ν 3532.2, 1459.6, 1207.4, 1094.4, 822.4 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{14}H_{12}O_2Cl$ [*M*-H]$^-$ 231.0577, found 231.0574.

3,6-Dimethyl-4'-nitro-[1,1'-biphenyl]-2-ol (3k)



Phenol **3k** was synthesized following the general procedure, starting from 1-ethynyl-4-nitrobenzene (35.0 mg, 0.23 mmol) and 2,5-dimethylfuran (44.8 mg, 0.46 mmol). The residue was purified by column chromatography (40:1 cyclohexane/EtOAc) to give compound **3k** (20.6 mg, 37%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.25 (m, 2H), 7.58 – 7.42 (m, 2H), 7.09 (d, *J* = 7.7 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 4.49 (s, 1H), 2.26 (s, 3H), 2.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.5 (C), 147.7 (C), 143.9 (C), 134.3 (C), 131.6 (CH), 130.8 (CH), 126.0 (C), 124.4 (CH), 122.2 (CH), 121.8 (C), 20.3 (CH_3), 15.9 (CH_3); IR (thin film) ν 3516.7, 2920.3, 1595.6, 1515.2, 1286.2, 1159.2, 1086.9, 872.2, 809.8, 706.2 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{14}H_{12}NO_3$ [*M*-H]$^-$ 242.0817, found 242.0810.

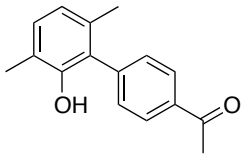
4'-Bromo-3,6-dimethyl-[1,1'-biphenyl]-2-ol (3l)



Phenol **3l** was synthesized following the general procedure 2, starting from 1-bromo-4-ethynylbenzene (34.7 mg, 0.19 mmol) and 2,5-dimethylfuran (18.1 mg, 0.19 mmol). The residue was purified by column chromatography (40:1 cyclohexane/EtOAc) to give compound **3l** (26.0 mg, 50%) as an

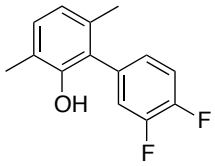
orange solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 7.6 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 4.64 (d, J = 0.5 Hz, 1H), 2.27 (s, 3H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.8 (C), 134.9 (C), 134.5 (C), 132.8 (CH), 132.2 (CH), 130.2 (CH), 126.5 (C), 122.5 (C), 121.7 (C), 121.7 (CH), 20.3 (CH_3), 16.0 (CH_3); IR (thin film) ν 3553.7, 2920.7, 1283.1, 1159.6, 1068.4, 938.9 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{14}H_{12}OBr$ [*M*-H]$^-$ 275.0072, found 275.0078.

1-(2'-Hydroxy-3',6'-dimethyl-[1,1'-biphenyl]-4-yl)ethanone (3m)



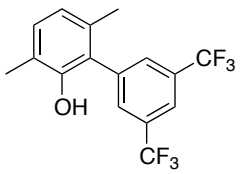
Phenol **3m** was synthesized following the general procedure, starting from 1-ethynyl-2-methylbenzene (35.0 mg, 0.24 mmol) and 2,5-dimethylfuran (46.2 mg, 0.48 mmol). The residue was purified by column chromatography (40:1 cyclohexane/EtOAc) to give compound **3m** (19.4 mg, 34%) as yellow solid: m.p. 159.1-174.6 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H), 7.06 (dd, J = 7.6, 0.8 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 4.65 (s, 1H), 2.66 (s, 3H), 2.26 (s, 3H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.7 (C), 150.5 (C), 141.3 (C), 136.6 (C), 134.1 (C), 137.7 (CH), 130.2 (CH), 129.3 (CH), 126.7 (CH), 121.7 (C), 121.7 (C), 29.9 (CH_3), 20.2 (CH_3), 15.9 (CH_3); IR (thin film) ν 3492.2, 2924.4, 1668.8, 1603.2, 1207.1, 1111.6, 803.4, 759.2 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{16}H_{15}O_2$ [*M*-H]$^-$ 239.1072, found 239.1083.

3',4'-Difluoro-3,6-dimethyl-[1,1'-biphenyl]-2-ol (3o)



Phenol **3o** was synthesized following the general procedure 2, starting from 4-ethynyl-1,2-difluorobenzene (45.8 mg, 0.30 mmol) and 2,5-dimethylfuran (57.9 mg, 0.60 mmol). The residue was purified by column chromatography (8:1 cyclohexane/EtOAc) to give compound **3o** (41.5 mg, 60%) as light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.21 (m, 1H), 7.15 (ddd, J = 10.8, 7.6, 2.1 Hz, 1H), 7.10 – 7.06 (m, 1H), 7.07 – 7.01 (m, 1H), 6.80 (d, J = 7.8 Hz, 1H), 4.63 (s, 1H), 2.28 (s, 2H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.6 (dd, J_{CF} = 84.1, 12.5 Hz, C), 150.9 (C), 149.6 (dd, J_{CF} = 83.2, 12.5 Hz, C), 134.6 (C), 132.90 (dd, J_{CF} = 5.9, 4.2 Hz, C), 130.4 (CH), 126.74 (dd, J = 6.2, 3.6 Hz, CH), 125.8 (C), 121.8 (C), 121.8 (CH), 119.7 (d, J_{CF} = 16.5 Hz, CH)), 118.42 (d, J_{CF} = 17.0 Hz, CH), 20.2 (CH_3), 16.0 (CH_3); IR (thin film) ν 3565.8, 2924.3, 1601.3, 1510.6, 1185.9, 1160.9, 1029.6, 1007.9, 801.9, 775.7 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{14}H_{11}OF_2$ $[M\text{-}H]^-$ 233.0778, found 233.0785.

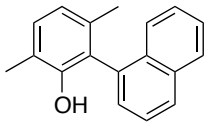
3,6-Dimethyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-ol (3p)



Phenol **3p** was synthesized following the general procedure 2, starting from 1-ethynyl-3,5-bis(trifluoromethyl)benzene (54.0 mg, 0.22 mmol) and 2,5-dimethylfuran (42.0 mg, 0.44 mmol). The residue was purified by column chromatography (50:1 cyclohexane/EtOAc) to give compound **3p** (17.7 mg, 48%) as a orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dt, J = 1.7, 0.9 Hz, 1H), 7.90 – 7.60 (m, 2H), 7.12 (dd, J = 7.7, 0.8 Hz, 1H), 6.84 (d, J = 7.7

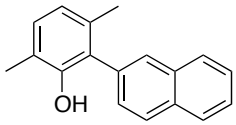
Hz, 1H), 4.48 (s, 1H), 2.29 (s, 3H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.8 (C), 139.1 (C), 134.7 (C), 132.4 (q, J_{CF} = 33.5 Hz, C), 130.9 (CH), 130.93 – 130.85 (m, C), 125.3 (C), 124.8 (C), 122.4 (CH), 122.1 (C), 121.8 (p, J_{CF} = 3.8 Hz, C), 121.6 (CH), 20.3 (CH_3), 15.9 (CH_3);); IR (thin film) ν 3588.6, 2927.3, 1386.5, 1212.4, 1105.6, 1094.4, 845.6, 695.6 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{16}H_{11}OF_6$ [*M*-H]$^-$ 333.0714, found 333.0711.

3,6-Dimethyl-2-(naphthalen-1-yl)phenol (3q)



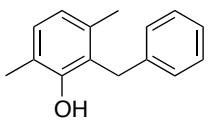
Phenol **3q** was synthesized following the general procedure 2, starting from 1-ethynylnaphthalene (29.2 mg, 0.19 mmol) and 2,5-dimethylfuran (18.1 mg, 0.19 mmol). The residue was purified by column chromatography (10:1 cyclohexane:EtOAc) to give compound **3q** (34.2 mg, 74%) as a orange solid: m.p. 72.0-79.6 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (ddt, *J* = 8.3, 4.1, 1.0 Hz, 2H), 7.60 (dd, *J* = 8.3, 7.0 Hz, 1H), 7.56 – 7.53 (m, 1H), 7.53 – 7.49 (m, 1H), 7.44 (dd, *J* = 6.9, 1.3 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 4.59 (d, *J* = 0.6 Hz, 1H), 2.31 (s, 3H), 1.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.5 (C), 135.6 (C), 134.3 (C),133.2 (C), 132.4 (C), 130.2 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 126.9 (CH), 126.6 (CH), 126.1 (CH), 125.5 (CH), 125.4 (C), 121.6 (C), 121.5 (CH), 20.0 (CH_3), 16.1 (CH_3); IR (thin film) ν 3492.9, 2954.3, 1221.2, 1183.7, 1042.9, 1012.2, 806.2, 786.5, 774.2 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{18}H_{15}O$ [*M*-H]$^-$ 247.1123, found 247.1132.

3,6-Dimethyl-2-(naphthalen-2-yl)phenol (3r)



Phenol **3r** was synthesized following the general procedure 2, starting from 2-ethynylnaphthalene (35.0 mg, 0.23 mmol) and 2,5-dimethylfuran (44.7 mg, 0.46 mmol). The residue was purified by column chromatography (10:1 cyclohexane:EtOAc) to give compound **3r** (26.6 mg, 47%) as a yellow solid: m.p. 70.3-72.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.3 Hz, 1H), 7.94 – 7.88 (m, 1H), 7.87 – 7.83 (m, 1H), 7.78 (d, J = 1.7 Hz, 1H), 7.61 – 7.42 (m, 2H), 7.38 (dd, J = 8.4, 1.7 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 4.85 (s, 1H), 2.27 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.1 (C), 133.9 (C), 133.3 (C), 133.0 (C), 130.0 (C), 129.5 (CH), 129.4 (CH),128.3 (CH), 128.1 (CH), 127.9 (CH), 127.5 (C), 126.7 (CH), 126.7 (CH), 121.7 (C), 121.6 (CH), 20.4 (CH_3), 16.1 (CH_3); IR (thin film) ν 3559.6, 2970.2, 1208.0, 1129.5, 826.2, 730.0 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{18}H_{15}O$ [*M*-H]$^-$ 247.1127, found 247.1123.

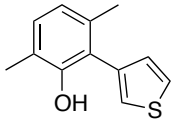
2-Benzyl-3,6-dimethylphenol (3s)



Phenol **3s** was synthesized following the general procedure 2, starting from prop-2-yn-1-ylbenzene (37.4 mg, 0.31 mmol) and 2,5-dimethylfuran (60.6 mg, 0.62 mmol). The residue was purified by column chromatography (40:1 cyclohexane:EtOAc) to give compound **3s** (27.6 mg, 42%) as a yellow solid: m.p. 62.7-69.4 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 2H), 7.21 – 7.09 (m, 3H), 6.94 (d, J = 7.6 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 4.58 (s, 1H), 4.05 (s, 1H), 2.26 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.5 (C), 139.8 (C), 136.1 (C), 128.7 (CH), 128.6 (CH), 128.2 (CH), 126.2 (CH), 124.8 (C), 122.4 (CH), 121.0 (C), 32.3 (CH_2), 19.9

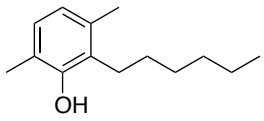
(CH_3), 16.1 (CH_3); IR (thin film) ν 3448.6, 2980.4, 1491.9, 1452.0, 1219.2, 1171.5, 1047.6, 800.7, 693.76 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{20}H_{23}O$ [*M*-H]$^-$ 279.1749, found 279.1738.

3,6-Dimethyl-2-(thiophen-3-yl)phenol (3t)



Phenol **3t** was synthesized following the general procedure 2, starting from ethynylcyclopropane (23.9 mg, 0.35 mmol) and 2,5-dimethylfuran (68.8 mg, 0.71 mmol). The residue was purified by column chromatography (50:1 cyclohexane:EtOAc) to give compound **3t** (10.9 mg, 19%) as a orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.33 – 7.23 (m, 1H), 7.08 (dd, *J* = 4.9, 1.3 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 5.05 (d, *J* = 0.5 Hz, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.6 (C), 135.7 (C), 135.3 (C), 130.1 (CH), 129.4 (CH), 127.5 (CH), 124.7 (CH), 122.4 (C), 121.5 (C),121.4 (CH), 20.3 (CH_3), 16.1 (CH_3); IR (thin film) ν 3495.2, 2964.7, 1711.1, 1354.9, 791.4, 728.9 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{12}H_{11}OS$ [*M*-H]$^-$ 203.0531, found 203.0525.

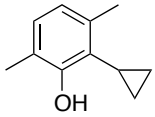
2-Hexyl-3,6-dimethylphenol (3v)



Phenol **3v** was synthesized following the general procedure 2, starting from oct-1-yne (22.9 mg, 0.35 mmol) and 2,5-dimethylfuran (40 mg, 0.42 mmol). The residue was purified by column chromatography (99:1 Pentane:EtOAc) to give compound **3v** (37 mg, 86%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, *J* = 7.6 Hz, 1 H), 6.67 (d, *J* = 7.6 Hz, 1 H), 4.59 (s, 1 H), 2.63-2.59 (m, 2 H), 2.28 (s, 3 H), 2.22 (s, 3 H), 1.53–1.38 (m, 2 H), 1.44–1.38 (m, 2 H), 1.36–1.30 (m, 4 H), 0.93–0.89 (m, 3 H); ^{13}C

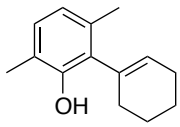
NMR ($CDCl_3$, 125 MHz) δ 151.8 (C), 135.1 (C), 127.6 (CH), 126.8 (C), 122.1 (CH), 120.4 (C), 31.8 (CH_2), 29.8 (CH_2), 29.2 (CH_2), 26.7 (CH_2), 22.7 (CH_2), 19.4 (CH_3), 15.8 (CH_3), 14.1 (CH_3).

2-Cyclopropyl-3,6-dimethylphenol (3w)



Phenol **3w** was synthesized following the general procedure 2, starting from ethynylcyclopropane (23.9 mg, 0.35 mmol) and 2,5-dimethylfuran (68.8 mg, 0.71 mmol). The residue was purified by column chromatography (50:1 cyclohexane:EtOAc) to give compound **3w** (10.9 mg, 19%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, J = 7.5 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 6.02 (s, 1H), 2.37 (s, 3H), 2.21 (s, 3H), 1.66 – 1.55 (m, 1H), 1.18 – 0.98 (dq, J = 6.6, 3.1 Hz, 2H), 0.78 – 0.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.7 (C), 137.1 (C), 129.0 (CH), 123.7 (C), 121.4 (CH), 121.3 (C), 19.7 (CH_3), 15.8 (CH_3), 7.5 (CH), 6.5 (CH_2); IR (thin film) ν 3495.8, 2924.3, 1721.3, 1461.3, 1217.1, 1018.1 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{11}H_{13}O$ [*M*-H]$^-$ 161.0966, found 161.0971.

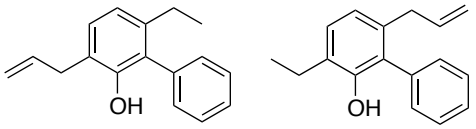
3,6-Dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-ol (3y)



Phenol **3y** was synthesized following the general procedure 2, starting from 1-ethynylcyclohexene (22.1 mg, 0.21 mmol) and 2,5-dimethylfuran (40 mg, 0.42 mmol). The residue was purified by column chromatography (99:1 pentane:EtOAc) to give compound **3y** (19 mg, 45%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (d, J = 7.6 Hz, 1 H), 6.65 (d, J = 7.6 Hz, 1 H), 5.79–5.76 (m, 1 H), 5.44 (d, J = 0.6 Hz, 1 H), 2.25–2.20 (m, 2 H), 2.21 (s, 3 H), 2.18–2.13 (m, 1 H), 2.17 (s, 3 H), 1.82–1.68 (m, 4 H); ^{13}C NMR

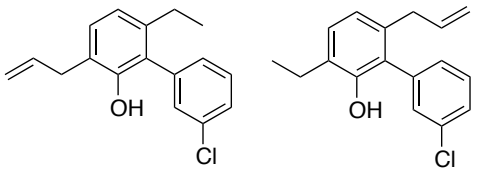
($CDCl_3$, 125 MHz) δ 150.0 (C), 134.4 (C), 133.6 (C), 129.9 (CH), 129.4 (C), 128.9 (CH), 121.0 (CH), 120.9 (C), 29.1 (CH_2), 25.5 (CH_2), 22.9 (CH_2), 22.1 (CH_2), 19.0 (CH_3), 15.9 (CH_3).

3-Allyl-6-ethyl-[1,1'-biphenyl]-2-ol and 6-allyl-3-ethyl-[1,1'-biphenyl]-2-ol (7ab + 7ab')



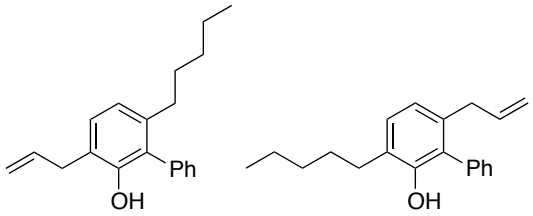
Phenol **7ab** and **7ab'** were synthesized following the general procedure 2, starting from ethynylbenzene (0.02 mL, 0.18 mmol) and 2-allyl-5-ethylfuran (49.6 mg, 0.36 mmol). The residue was purified by automated flash chromatography (4 g RediSep flash column, cyclohexane/EtOAc 16 min gradient 5% EtOAc) to give a mixture of products **7ab** and **7ab**' in 0.8:1 ratio (16.8 mg, 39%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.37 (m, 6H), 7.37 – 7.24 (m, 4H), 7.10 (dd, J = 7.8, 6.2 Hz, 2H), 6.83 (t, J = 7.4 Hz, 2H), 6.04 (ddt, J = 16.8, 10.0, 6.6 Hz, 1H), 5.79 (ddt, J = 16.8, 10.0, 6.6 Hz, 1H), 5.22 – 5.03 (m, 2H), 4.98 – 4.88 (m, 1H), 4.82 (dd, J = 17.0, 1.8 Hz, 1H), 4.76 (s, 1H), 4.73 (s, 1H), 3.41 (dt, J = 6.8, 1.5 Hz, 2H), 3.08 (dt, J = 6.7, 1.5 Hz, 2H), 2.66 (q, J = 7.5 Hz, 2H), 2.35 (q, J = 7.5 Hz, 2H), 1.24 (t, J = 7.5 Hz, 3H), 1.02 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.7 (C), 150.6 (C), 141.4 (C), 137.6 (CH), 137.1 (CH), 136.4 (C), 135.5 (C), 135.3 (C), 130.7 (CH), 130.7 (CH), 129.5 (CH), 129.5 (CH), 129.3 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.1 (C), 127.7 (C), 127.7 (C), 123.5 (C), 121.0 (CH), 120.1 (CH), 115.7 (CH_2), 115.6 (CH_2), 37.8 (CH_2), 34.7 (CH_2), 26.5 (CH_2), 23.3 (CH_2), 15.6 (CH_3), 14.16 (CH_3); IR (thin film) ν 3588.6, 2927.3, 1310.4, 1183.3, 1094.4, 888.9 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{17}H_{17}O$ $[M\text{-}H]^-$ 237.1279, found 237.1283.

3-Allyl-3'-chloro-6-ethyl-[1,1'-biphenyl]-2-ol and 6-allyl-3'-chloro-3-ethyl-[1,1'-biphenyl]-2-ol (7fb + 7fb')



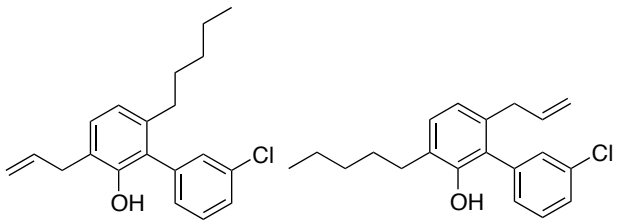
Phenol **7fb** and **7fb'** were synthesized following the general procedure 2, starting from 1-chloro-3-ethynylbenzene (0.02 mL, 0.16 mmol) and 2-allyl-5-ethylfuran (44.2 mg, 0.33 mmol). The residue was purified by automated flash chromatography (4 g RediSep flash column, cyclohexane/EtOAc 16 min gradient 5% EtOAc) to give a mixture of products **7fb** and **7fb'** in 0.8:1 ratio (23.3 mg, 53%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.37 (m, 4H), 7.30 (t, J = 1.4 Hz, 2H), 7.23 – 7.14 (m, 2H), 7.11 (t, J = 7.2 Hz, 2H), 6.83 (t, J = 7.5 Hz, 2H), 6.14 – 5.93 (m, 1H), 5.78 (ddt, J = 16.7, 10.2, 6.5 Hz, 1H), 5.23 – 5.04 (m, 2H), 5.02 – 4.89 (m, 1H), 4.82 (dd, J = 17.0, 1.7 Hz, 1H), 4.71 (s, 1H), 4.61 (s, 1H), 3.40 (dd, J = 6.7, 1.7 Hz, 2H), 3.07 (dt, J = 6.5, 1.6 Hz, 2H), 2.65 (q, J = 7.5 Hz, 2H), 2.34 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.5 Hz, 3H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.6 (C), 150.5 (C), 141.4 (C), 137.7 (C), 137.4 (CH), 136.9 (CH) 136.3 (C), 135.3 (C), 135.2 (C), 130.9 (CH), 130.7 (CH), 130.7 (CH), 130.6 (CH), 129.8 (CH), 128.9 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.3 (C), 126.5 (C), 126. (C), 123.5 (C), 121.2 (CH), 120.3 (CH), 116.0 (CH_2), 115.8 (CH_2), 37.8 (CH_2), 34.8 (CH_2), 26.5 (CH_2), 23.3 (CH_2), 15.5 (CH_3), 14.1 (CH_3) (one carbon signal is missing due to overlapping); IR (thin film) ν 3564.1, 2964.1, 2930.9, 1613.0, 1471.2, 1195.3, 790.2, 701.4 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{17}H_{16}OCl$ $[M\text{-}H]^-$ 271.0890, found 271.0891.

6-Allyl-3-pentyl-[1,1'-biphenyl]-2-ol and 3-allyl-6-pentyl-[1,1'-biphenyl]-2-ol (7ac + 7ac')



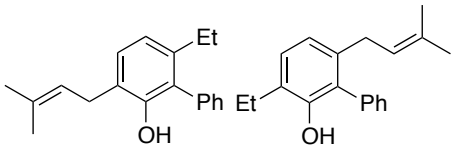
Phenol **7ac** and **7ac'** were synthesized following the general procedure 2, starting from ethynylbenzene (0.02 mL, 0.18 mmol) and 2-allyl-5-pentylfuran (64.9 mg, 0.36 mmol). The residue was purified by automated flash chromatography (4 g RediSep flash column, cyclohexane/EtOAc 16 min gradient 5% EtOAc) to give a mixture of products **7ac** and **7ac'** in 1:1 ratio (19.0 mg, 37%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.35 (m, 6H), 7.35 – 7.21 (m, 4H), 7.08 (dd, J = 7.8, 5.3 Hz, 2H), 6.81 (dd, J = 7.8, 5.8 Hz, 2H), 6.04 (ddt, J = 16.8, 10.1, 6.6 Hz, 1H), 5.79 (ddt, J = 16.7, 10.1, 6.6 Hz, 1H), 5.24 – 5.01 (m, 2H), 4.98 – 4.88 (m, 1H), 4.82 (dd, J = 17.0, 1.8 Hz, 1H), 4.76 (s, 1H), 4.71 (s, 1H), 3.40 (dd, J = 6.8, 1.6 Hz, 2H), 3.08 (dt, J = 6.7, 1.6 Hz, 2H), 2.61 (dd, J = 8.9, 6.7 Hz, 2H), 2.42 – 2.21 (m, 2H), 1.37 – 1.33 (m, 4H), 1.16 – 1.11 (m, 4H), 1.01 – 0.84 (m, 3H), 0.76 (t, J = 6.5, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.7 (C), 150.7 (C), 140.2 (C), 137.6 (CH), 137.1 (CH), 136.4 (C), 135.5 (C), 135.3 (C), 130.8 (CH), 130.7 (CH), 129.5 (CH), 129.4 (CH), 129.3 (CH), 128.4 (CH), 128.3 (CH), 127.9 (C), 127.7 (C), 126.9 (C), 123.4 (C), 120.9 (CH), 115.7 (CH_2), 115.7 (CH_2), 37.9 (CH_2), 34.7 (CH_2), 33.3 (CH_2), 32.0 (CH_2), 31.8 (CH_2), 30.3 (CH2), 29.7 (CH_2), 22.8 (CH_2), 22.5 (CH_2), 14.2 (CH_3), 14.1 (CH_3); IR (thin film) ν 3550.1, 2927.2, 2856.9, 1441.9, 703.8 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{15}H_{15}O$ [*M*-H]$^-$ 211.1123, found 211.1108.

3-Allyl-3'-chloro-6-pentyl-[1,1'-biphenyl]-2-ol and 6-allyl-3'-chloro-3-pentyl-[1,1'-biphenyl]-2-ol (7fc + 7af')



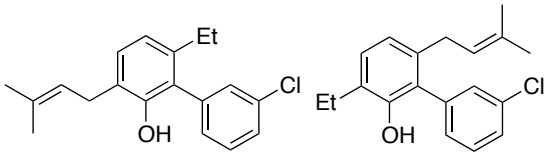
Phenol **7fc** and **7fc'** were synthesized following the general procedure 2, starting from 1-chloro-3-ethynylbenzene (0.02 mL, 0.16 mmol) and 2-allyl-5-pentylfuran (57.9 mg, 0.33 mmol). The residue was purified by automated flash chromatography (4 g RediSep flash column, cyclohexane/EtOAc 16 min gradient 5% EtOAc) to give a mixture of products **7fc** and **7fc'** in 0.95:1 ratio (45.0 mg, 90%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.40 (m, 4H), 7.33 (d, J = 2.5 Hz, 2H), 7.21 (td, J = 4.2, 2.0 Hz, 2H), 7.12 (dd, J = 7.8, 5.6 Hz, 2H), 6.83 (dd, J = 7.8, 6.2 Hz, 2H), 6.06 (ddt, J = 16.8, 10.0, 6.6 Hz, 1H), 5.81 (ddt, J = 16.7, 10.0, 6.5 Hz, 1H), 5.25 – 5.06 (m, 2H), 4.98 (dd, J = 10.1, 1.7 Hz, 1H), 4.85 (dd, J = 17.0, 1.8 Hz, 1H), 4.73 (s, 1H), 4.63 (s, 1H), 3.43 (dt, J = 6.8, 1.5 Hz, 2H), 3.10 (dt, J = 6.6, 1.6 Hz, 2H), 2.79 – 2.54 (m, 2H), 2.47 – 2.24 (m, 2H), 1.42 - 1.37 (m, 4H), 1.26 – 1.12 (m, 4H), 1.02 – 0.88 (m, 3H), 0.82 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.6 (C), 150.6 (C), 140.2 (C), 137.8 (C), 137.4 (C), 137.4 (CH), 137.0 (CH), 136.3 (C), 135.3 (C), 135.2 (C), 130.91 (CH), 130.8 (CH), 130.7 (CH), 130.5 (CH), 129.7 (CH), 129.6 (CH), 129.0 (CH), 128.9 (CH), 128.6 (CH), 128.4 (CH), 127.1 (C), 126.7 (C), 126.5 (C), 123.5 (C), 121.1 (CH), 121.1 (CH), 116.0 (CH_2), 115.8 (CH_2), 37.8 (CH_2), 34.9 (CH_2), 33.3 (CH_2), 32.0 (CH_2), 31.7 (CH_2), 30.9 (CH_2), 30.3 (CH_2), 29.6 (CH_2), 22.7 (CH_2), 22.4 (CH_2), 14.2 (CH_3), 14.0 (CH_3); IR (thin film) ν 2927.4, 1562.7, 1214.3, 788.6, 701.5 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{20}H_{22}OCl$ [*M*-H]$^-$ 313.1359, found 313.1362.

6-Ethyl-3-(3-methylbut-2-en-1-yl)-[1,1'-biphenyl]-2-ol and 3-Ethyl-6-(3-methylbut-2-en-1-yl)-[1,1'-biphenyl]-2-ol (7ad + 7ad')



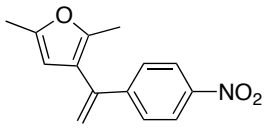
Phenol **7ad** and **7ad'** were synthesized following the general procedure 2, starting from 1-chloro-3-ethynylbenzene (0.02 mL, 0.18 mmol) and 2-ethyl-5-(3-methylbut-2-en-1-yl)furan (59.8 mg, 0.36 mmol). The residue was purified by automated flash chromatography (4 g RediSep flash column, cyclohexane/EtOAc 16 min gradient 5% EtOAc) to give a mixture of products **7ad** and **7ad'** in 1:2 ratio (30.0 mg, 62%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.45 (m, 6H), 7.45 – 7.36 (m, 2H), 7.30 – 7.27 (m, 2H), 7.09 (dd, J = 7.8, 6.0 Hz, 2H), 6.81 (t, J = 7.3 Hz, 2H), 5.36 (ddt, J = 8.8, 5.9, 1.4 Hz, 1H), 5.09 (ddt, J = 8.7, 5.8, 1.4 Hz, 1H), 4.82 (d, J = 0.5 Hz, 1H), 4.70 (d, J = 0.6 Hz, 1H), 3.40 – 3.26 (m, 2H), 3.02 (d, J = 7.3 Hz, 2H), 2.65 (q, J = 7.5 Hz, 2H), 2.34 (q, J = 7.6 Hz, 2H), 1.75 (d, J = 1.3 Hz, 3H), 1.73 (d, J = 1.5 Hz, 3H), 1.62 (d, J = 1.3 Hz, 3H), 1.38 (s, 3H), 1.24 (t, J = 7.6 Hz, 3H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.8 (C), 150.6 (C), 141.1 (C), 138.3 (C), 135.8 (C), 135.4 (C), 133.1 (C), 131.8 (C), 130.8 (CH), 130.6 (CH), 129.5 (CH), 129.4 (CH), 128.9 (C), 128.4 (CH), 128.3 (CH), 128.1 (C), 127.7 (C), 127.6 (C), 123.5 (CH), 122.6 (CH), 120.6 (CH), 120.0 (CH), 32.4 (CH_2), 29.0 (CH_2), 26.4 (CH_2), 26.0 (CH_2), 25.8 (CH_3), 23.3 (CH_3), 17.9 (CH_3), 17.6 (CH_3), 15.6 (CH_3), 14.2 (CH_3); IR (thin film) ν 2974.5, 2938.4, 1698.8, 1461.9, 1378.3, 1111.3, 758.5, 697.7 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{19}H_{21}O$ [*M*-H]$^-$ 265.1592, found 265.1605.

3'-Chloro-6-ethyl-3-(3-methylbut-2-en-1-yl)-[1,1'-biphenyl]-2-ol and 3'-chloro-3-ethyl-6-(3-methylbut-2-en-1-yl)-[1,1'-biphenyl]-2-ol (7fd + 7fd')



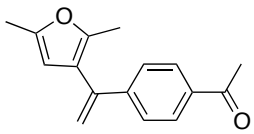
Phenol **7fd** and **7fd'** were synthesized following the general procedure, starting from 1-chloro-3-ethynylbenzene (0.02 mL, 0.16 mmol) and 2-ethyl-5-(3-methylbut-2-en-1-yl)furan (53.3 mg, 0.33 mmol). The residue was purified by automated flash chromatography (4 g RediSep flash column, cyclohexane/EtOAc 16 min gradient 5% EtOAc) to give a mixture of products **7fd** and **7fd'** in 1:2 ratio (32.9 mg, 67%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.40 (m, 4H), 7.33 (td, J = 2.1, 0.9 Hz, 2H), 7.22 (dd, J = 7.0, 1.6 Hz, 2H), 7.14 (t, J = 7.8 Hz, 2H), 6.85 (dd, J = 7.8, 6.0 Hz, 2H), 5.38 (tt, J = 7.3, 1.4 Hz, 1H), 5.11 (tt, J = 7.2, 1.4 Hz, 1H), 4.86 (s, 1H), 4.62 (d, J = 0.6 Hz, 1H), 3.39 (d, J = 7.3 Hz, 2H), 3.04 (d, J = 7.2 Hz, 2H), 2.68 (q, J = 7.6 Hz, 2H), 2.38 (q, J = 7.6 Hz, 2H), 1.79 (d, J = 1.3 Hz, 3H), 1.78 (s, 3H), 1.67 (d, J = 1.3 Hz, 3H), 1.44 – 1.40 (m, 3H), 1.27 (t, J = 7.5 Hz, 3H), 1.06 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.8 (C), 150.4 (C), 141.1 (C), 138.2 (C), 138.1 (C), 137.5 (C), 135.3 (C), 135.1 (C), 133.7 (C), 132.0 (C), 131.1 (CH), 130.7 (CH), 130.6 (CH), 130.4 (CH), 129.4 (C), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 126.6 (C), 126.3 (C), 124.9 (C), 123.3 (CH), 122.3 (CH), 120.9 (CH), 120.2 (CH), 32.5 (CH_2), 29.3 (CH_2), 26.4 (CH_2), 26.0 (CH_3), 25.8 (CH_3), 23.3 (CH_2), 18.0 (CH_3), 17.6 (CH_3), 15.5 (CH_3), 14.1 (CH_3) ; IR (thin film) ν 2975.9, 2925.2, 1650.8, 1562.4, 1423.1, 1096.7, 784.2 cm^{-1}; HRMS-ESI *m/z* calculated for $C_{19}H_{20}OCl$ $[M\text{-}H]^-$ 299.1203, found 299.1195.

2,5-Dimethyl-3-(1-(4-nitrophenyl)vinyl)furan (4k)



Furan **4k** was synthesized following the general procedure 2 as secondary product, starting from 1-ethynyl-4-nitrobenzene (35.0 mg, 0.23 mmol) and 2,5-dimethylfuran (44.8 mg, 0.46 mmol). The residue was purified by column chromatography (40:1 cyclohexane/EtOAc) to give compound **4k** (12.3 mg, 22%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.14 (m, 2H), 7.60 – 7.50 (m, 2H), 5.82 (d, J = 1.2 Hz, 1H), 5.56 (d, J = 1.1 Hz, 1H), 5.40 (d, J = 1.1 Hz, 1H), 2.28 (s, 3H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.3 (C), 147.9 (C), 147.4 (C), 140.8 (C), 129.1 (C), 128.7 (CH), 123.7 (CH), 116.9 (CH_2), 107.5 (CH), 82.5 (CH_2), 13.5 (CH_3), 13.0 (CH_3).

1-(4-(1-(2,5-Dimethylfuran-3-yl)vinyl)phenyl)ethanone (4m)

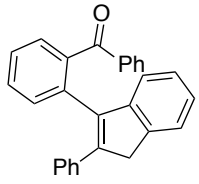


Furan **4m** was synthesized following the general procedure 1 as secondary product, starting from 1-ethynyl-2-methylbenzene (35.0 mg, 0.24 mmol) and 2,5-dimethylfuran (46.2 mg, 0.48 mmol). The residue was purified by column chromatography (40:1 cyclohexane/EtOAc) to give compound **4m** (13.2 mg, 23%) as light yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.64 (m, 2H), 7.66 – 7.35 (m, 2H), 5.83 (d, J = 1.1 Hz, 1H), 5.49 (d, J = 1.4 Hz, 1H), 5.31 (d, J = 1.4 Hz, 1H), 2.61 (s, 3H), 2.25 (d, J = 0.5 Hz, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.9 (C), 149.7 (C), 147.9 (C), 146.1 (C), 141.6 (C), 136.4 (C), 128.5 (CH), 127.8 (CH), 120.9 (C), 115.6 (CH), 107.7 (CH), 26.8 (CH_3),

13.5 (CH_3), 13.1 (CH_3); HRMS-ESI *m/z* calculated for $C_{16}H_{17}O_2$ [*M*-H]$^-$ 241.1229, found 241.1218.

General procedure 3: synthesis of indenes: A solution of gold(I) catalyst (3mol%) in dry CH_2Cl_2 (0.2 mL) was added to a solution of the corresponding acetylene (1 equiv) and 1,3-diphenylisobenzofuran (2 equiv) in dry CH_2Cl_2 (0.2 mL). The reaction was stirred at room temperature for 12 h. Then, 10 drops of triethylamine were added and the mixture was stirred for 30 min. The solvent was removed under vacuum and the crude was purified by column chromatography to give the corresponding indene.

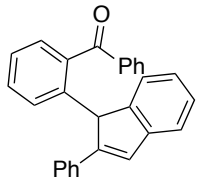
Phenyl(2-(2-phenyl-1*H*-inden-3-yl)phenyl)methanone (11a)



Indene **11a** was synthesized following the general procedure 3 as the major product, starting from ethynylbenzene (18.6 mg, 0.18 mmol) and 1,3-diphenylisobenzofuran (99.0 mg, 0.36 mmol). The residue was purified by column chromatography (50:1 cyclohexane/EtOAc) to give compound **11a** (38.8 mg, 70%) as light yellow foamy solid: mp 68-74 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (td, *J* = 7.5, 1.4 Hz, 1H), 7.59 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.55 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.49 (td, *J* = 7.5, 1.3 Hz, 1H), 7.35 – 7.29 (m, 3H), 7.24 – 7.20 (m, 2H), 7.17 – 7.14 (dt, *J* = 6.8, 1.8 Hz, 5H), 7.09 – 7.04 (m, 2H), 7.03 – 7.00 (m, 2H), 3.50 (q, *J* = 22.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.1 (C), 146.9 (C), 143.5 (C), 142.2 (C), 139.4 (C), 138.4 (C), 137.6 (C), 136.1 (C), 135.9 (C), 131.9 (CH), 131.4 (CH), 130.7 (CH), 130.4 (CH), 128.9 (CH), 128.4 (CH), 128.2 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 126.5 (CH), 125.1 (CH), 123.5 (CH), 120.4

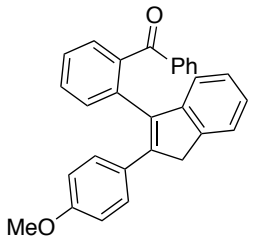
(CH), 40.8 (CH_2); HRMS-ESI *m/z* calculated for $C_{28}H_{20}ONa$ $[M+Na]^+$ 395.1412, found 395.1405.

Phenyl(2-(2-phenyl-1*H*-inden-1-yl)phenyl)methanone (11a')



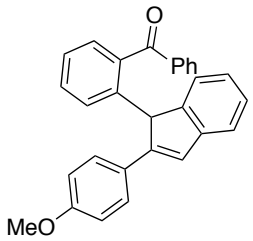
Indene **11a'** was synthesized following the general procedure 3 as the minor product, starting from ethynylbenzene (18.6 mg, 0.18 mmol) and 1,3-diphenylisobenzofuran (99.0 mg, 0.36 mmol). The residue was purified by column chromatography (50:1 cyclohexane/EtOAc) to give compound **11a'** (17.0 mg, 30%) as light yellow solid: mp 145-152 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 7.7 Hz, 2H), 7.68 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.6 Hz, 2H), 7.54 – 7.45 (m, 2H), 7.43 – 7.38 (m, 2H), 7.36 – 7.33 (m, 2H), 7.22 – 7.17 (m, 3H), 7.16 – 7.14 (m, 2H), 7.09 (td, J = 7.4, 1.1 Hz, 1H), 6.78 (d, J = 6.9 Hz, 1H), 5.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 183.6 (C), 133.6 (CH), 131.3 (CH), 130.9 (CH), 129.5 (CH), 128.7 (CH), 128.6 (CH), 128.0 (CH), 127.4 (CHH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 125.7 (CH), 124.6 (CH), 122.6 (CH), 121.2 (CH), 51.6 (CH); HRMS-ESI *m/z* calculated for $C_{28}H_{20}ONa$ $[M+Na]^+$ 395.1412, found 395.1399.

(2-(2-(4-Methoxyphenyl)-1*H*-inden-3-yl)phenyl)(phenyl)methanone (11b)



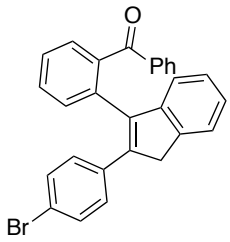
Indene **11b** was synthesized following the general procedure 3 as the major product, starting from 1-ethynyl-4-methoxybenzene (10.2 mg, 0.08 mmol) and 1,3-diphenylisobenzofuran (43.0 mg, 0.15 mmol). The residue was purified by column chromatography (50:1 cyclohexane/EtOAc) to give compound **11b** (42.9 mg, 68%) as orange solid: mp 154-158 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (td, J = 7.5, 1.4 Hz, 1H), 7.60 (dd, J = 7.5, 1.6 Hz, 1H), 7.54 (dd, J = 7.6, 1.2 Hz, 1H), 7.49 (td, J = 7.5, 1.3 Hz, 1H), 7.33 (dd, J = 8.2, 1.4 Hz, 2H), 7.31 – 7.26 (m, 1H), 7.25 – 7.16 (m, 2H), 7.14 – 7.09 (m, 2H), 7.04 – 6.95 (m, 4H), 6.72 – 6.64 (m, 2H), 3.74 (s, 3H), 3.57 – 3.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.2 (C), 158.9 (C), 147.2 (C), 143.3 (C),141.9 (C), 139.4 (C), 137.6 (C), 136.7 (C), 136.1 (C), 131.9 (CH), 131.4 (CH), 130.8 (CH), 130.3 (CH), 129.9 (C), 129.3 (CH), 128.9 (CH), 127.5 (CH), 127.5 (CH), 126.4 (CH), 124.7 (CH), 123.3 (CH), 120.1 (CH), 113.8 (CH), 55.23 (CH_3), 40.8 (CH_2); HRMS-ESI *m/z* calculated for $C_{29}H_{22}O_2Na$ $[M+Na]^+$ 425.1517, found 425.1526.

(2-(2-(4-Methoxyphenyl)-1*H*-inden-1-yl)phenyl)(phenyl)methanone (11b')



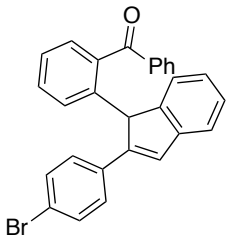
Indene **11b'** was synthesized following the general procedure 3 as the minor product, starting from 1-ethynyl-4-methoxybenzene (10.2 mg, 0.08 mmol) and 1,3-diphenylisobenzofuran (43.0 mg, 0.15 mmol). The residue was purified by column chromatography (50:1 cyclohexane/EtOAc) to give compound **11b'** (19.9 mg, 32%) as white solid: mp 155-158 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 – 7.97 (m, 2H), 7.68 (t, J = 7.0 Hz, 1H), 7.57 (t, J = 7.6 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.44 – 7.35 (m, 2H), 7.29 (d, J = 7.5 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.19 – 7.11 (m, 2H), 7.05 (td, J = 7.4, 1.1 Hz, 1H), 6.79 (dd, J = 7.5, 1.7 Hz, 2H), 6.75 (d, J = 8.8 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.4 (C), 159.1 (C), 150.9 (C), 149.6 (C), 143.9 (C), 140.0 (C), 138.5 (C), 138.1 (C), 133.6 (CH), 131.3 (CH), 130.9 (CH), 129.5 (CH), 128.3 (CH), 127.9 (C), 127.9 (CH), 127.1 (CH), 126.6 (CH), 125.6 (CH), 125.2 (CH), 124.4 (CH), 120.9 (CH), 114.0 (CH), 55.3 (CH_3), 51.6 (CH); HRMS-ESI *m/z* calculated for $C_{29}H_{22}O_2Na$ $[M+Na]^+$ 425.1517, found 425.1526.

(2-(2-(4-Bromophenyl)-1*H*-inden-3-yl)phenyl)(phenyl)methanone (11c)



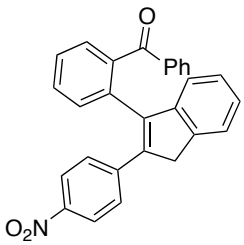
Indene **11c** was synthesized following the general procedure 3 as the major product, starting from 1-ethynyl-4-bromobenzene (20.0 mg, 0.11 mmol) and 1,3-diphenylisobenzofuran (61.6 mg, 0.22 mmol). The residue was purified by column chromatography (50:1 cyclohexane/EtOAc) to give compound **11c** (33.0 mg, 77%) as orange foamy solid: mp 131-137 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (td, J = 7.5, 1.4 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.55 – 7.52 (m, 1H), 7.50 (td, J = 7.5, 1.3 Hz, 1H), 7.37 – 7.36 (m, 1H), 7.35 – 7.33 (m, 2H), 7.28 (tt, J = 7.3, 1.3 Hz, 1H), 7.26 – 7.24 (m, 1H), 7.24 – 7.23 (m, 1H), 7.21 (dd, J = 7.5, 1.2 Hz, 1H), 7.17 (dd, J = 7.3, 1.3 Hz, 1H), 7.14 (dt, J = 7.5, 1.0 Hz, 1H), 7.10 – 7.05 (m, 2H), 6.93 – 6.88 (m, 2H), 3.55 (d, J = 22.4 Hz, 1H), 3.48 (d, J = 22.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.0 (C), 146.7 (C), 142.1 (C), 142.0 (C), 139.3 (C), 139.2 (C), 137.3 (C), 135.5 (C), 135.1 (C), 132.2 (CH), 131.5 (CH), 131.4 (CH), 130.7 (CH), 130.3 (CH), 129.7 (CH), 129.1 (CH), 127.7 (CH), 126.6 (CH), 125.4 (CH), 123.6 (CH), 121.4 (C), 120.5 (CH), 40.8 (CH_2); HRMS-ESI *m/z* calculated for $C_{28}H_{19}ONaBr$ $[M+Na]^+$ 473.0517, found 473.0513.

(2-(2-(4-Bromophenyl)-1*H*-inden-1-yl)phenyl)(phenyl)methanone (11c')



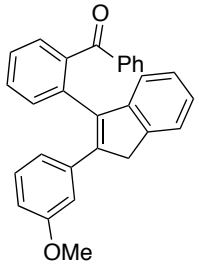
Indene **11c'** was synthesized following the general procedure 3 as the minor product, starting from 1-ethynyl-4-bromobenzene (20.0 mg, 0.11 mmol) and 1,3-diphenylisobenzofuran (61.6 mg, 0.22 mmol). The residue was purified by column chromatography (50:1 cyclohexane/EtOAc) to give compound **11c'** (11.4 mg, 23%) as yellow solid: mp 153-157 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 – 7.97 (m, 2H), 7.62 (q, J = 1.0 Hz, 3H), 7.60 – 7.55 (m, 2H), 7.54 – 7.49 (m, 3H), 7.44 – 7.40 (m, 2H), 7.35 – 7.32 (m, 2H), 7.31 – 7.28 (m, 2H), 7.09 (td, J = 7.5, 1.1 Hz, 1H), 6.73 (d, J = 7.7 Hz, 1H), 5.53 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.7 (C), 140.2 (C), 139.3 (C), 138.5 (C), 137.3 (C), 134.0 (C), 133.8 (C), 133.1 (CH), 131.7 (CH), 131.4 (C), 130.9 (CH), 130.5 (CH), 129.8 (CH), 129.1 (CH), 128.8 (C), 128.5 (CH), 127.8 (CH), 127.2 (CH), 125.9 (CH), 125.9 (CH), 124.6 (CH), 124.6 (CH), 121.4 (CH), 51.5 (CH); HRMS-ESI *m/z* calculated for $C_{28}H_{19}ONaBr$ $[M+Na]^+$ 473.0517, found 473.0517.

(2-(2-(4-Nitrophenyl)-1*H*-inden-3-yl)phenyl)(phenyl)methanone (11d)



Indene **11d** was synthesized following the general procedure 3, starting from 1-ethynyl-4-nitrobenzene (15.0 mg, 0.10 mmol) and 1,3-diphenylisobenzofuran (55.1 mg, 0.20 mmol). The residue was purified by column chromatography (50:1 cyclohexane/EtOAc) to give compound **11d** (20.7 mg, 49%) as orange solid: mp 131-134 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 8.9 Hz, 2H), 7.56 (dd, J = 7.5, 1.3 Hz, 1H), 7.54 – 7.48 (m, 5H), 7.40 (d, J = 1.2 Hz, 2H), 7.33 – 7.28 (m, 2H), 7.23 (d, J = 2.0 Hz, 1H), 7.22 – 7.19 (m, 2H), 7.09 (dd, J = 8.3, 7.4 Hz, 2H), 3.66 (d, J = 22.5 Hz, 1H), 3.58 (d, J = 22.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.7 (C), 146.3 (C), 142.9 (C), 140.6 (C), 140.2 (C), 139.2 (C), 137.3 (C), 134.9 (C), 133.13 (CH), 132.3 (C), 131.6 (C), 130.5 (CH), 130.5 (CH), 129.8 (CH), 129.2 (CH), 128.6 (CH), 128.2 (CH), 127.8 (CH), 126.9 (CH), 126.3 (CH), 123.8 (CH), 123.7 (CH), 121.13 (CH), 40.7 (CH_2); HRMS-ESI *m/z* calculated for $C_{28}H_{19}NO_3Na$ $[M+Na]^+$ 440.1263, found 440.1252.

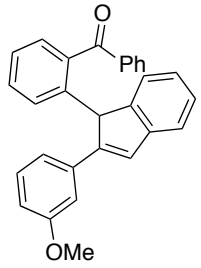
(2-(2-(3-Methoxyphenyl)-1*H*-inden-3-yl)phenyl)(phenyl)methanone (11e)



Indene **11e** was synthesized following the general procedure 3 as the major product, starting from 1-ethynyl-3-methoxybenzene (10.4 mg, 0.08 mmol)

and 1,3-diphenylisobenzofuran (43.9 mg, 0.16 mmol). The residue was purified by column chromatography (50:1 cyclohexane/EtOAc) to give compound **11e** (26.0 mg, 82%) as orange foamy solid: mp 137-141 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (td, J = 7.5, 1.4 Hz, 1H), 7.60 (dd, J = 7.7, 1.4 Hz, 1H), 7.55 (dd, J = 7.6, 1.3 Hz, 1H), 7.49 (td, J = 7.6, 1.3 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.34 – 7.30 (m, 1H), 7.26 – 7.23 (m, 1H), 7.22 – 7.19 (m, 1H), 7.18 – 7.12 (m, 2H), 7.08 (d, J = 7.9 Hz, 1H), 7.06 – 7.00 (m, 2H), 6.68 (dddd, J = 11.3, 7.6, 2.1, 0.9 Hz, 2H), 6.59 (dd, J = 2.6, 1.6 Hz, 1H), 3.56 (s, 3H), 3.56 (d, J = 22.4 Hz, 1H), 3.46 (d, J = 22.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197. 4 (C), 159.4 (C), 146.9 (C), 143.3 (C),142.1 (C), 139.5 (C), 138.8 (C), 137.5 (C), 137.3 (C), 135.9 (C), 132.0 (CH), 131.3 (CH), 130.7 (CH), 130.3 (CH), 129.3 (CH), 129.0 (CH), 127.6 (CH), 127.6 (CH), 126.5 (CH), 125.2 (CH), 123.5 (CH), 120.7 (CH), 120.4 (CH), 113.5 (CH), 113.4 (CH), 55.0 (CH_3), 40.8 (CH_2); HRMS-ESI *m/z* calculated for $C_{29}H_{22}O_2Na$ $[M+Na]^+$ 425.1517, found 425.1511.

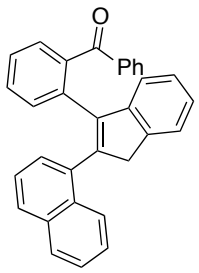
(2-(2-(3-Methoxyphenyl)-1*H*-inden-1-yl)phenyl)(phenyl)methanone (11e')



Indene **11e'** was synthesized following the general procedure 3 as the minor product, starting from 1-ethynyl-3-methoxybenzene (10.4 mg, 0.08 mmol) and 1,3-diphenylisobenzofuran (43.9 mg, 0.16 mmol). The residue was purified by column chromatography (50:1 cyclohexane/EtOAc) to give compound **11e'** (5.6 mg, 16%) as white solid: mp 139.6-148.3 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.6 Hz, 2H), 7.40 (d, J = 7.4 Hz, 2H), 7.36 – 7.32 (m, 1H), 7.28 (d, J

= 7.4 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.17 – 7.13 (m, 2H), 7.11- 7.10 (m, 2H), 7.07 (td, *J* = 7.5, 1.0 Hz, 1H), 6.84 – 6.76 (m, 2H), 6.71 (dt, *J* = 6.2, 2.6 Hz, 1H), 5.57 (s, 1H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.1 (C), 149.8 (C), 143.4 (C), 138.5 (C), 136.5 (C), 133.6 (CH), 131.9 (C), 131.7 (C), 131.3 (CH), 130.9 (CH), 130.2 (C), 129.5 (CH), 129.4 (CH), 128.8 (CH), 128.7 (CH), 127.8 (CH), 127.2 (CH), 127.1 (CH), 125.7 (CH), 124.5 (CH), 121.3 (CH), 119.6 (CH), 113.3 (CH), 112.6 (CH), 55.4 (CH_3), 51.7 (CH); HRMS-ESI *m/z* calculated for $C_{29}H_{22}O_2Na$ $[M+Na]^+$ 425.1517, found 425.1532.

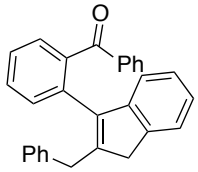
(2-(2-(Naphthalen-1-yl)-1*H*-inden-3-yl)phenyl)(phenyl)methanone (11g)



Indene **11g** was synthesized following the general procedure 3, starting from 1-ethynylnaphtalene (10.7 mg, 0.07 mmol) and 1,3-diphenylisobenzofuran (38.0 mg, 0.14 mmol). The residue was purified by column chromatography (50:1 cyclohexane/EtOAc) to give compound **11g** (27.0 mg, 90%) as orange foamy solid: mp 76-81 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.66 – 7.63 (m, 1H), 7.56 (tt, *J* = 8.3, 1.0 Hz, 2H), 7.49 – 7.46 (m, 1H), 7.46 – 7.43 (m, 1H), 7.34 – 7.31 (m, 1H), 7.30 – 7.27 (m, 2H), 7.27 – 7.23 (m, 2H), 7.21 – 7.19 (m, 2H), 7.18 – 7.12 (m, 4H), 7.11 – 7.08 (m, 1H), 7.06 (dd, *J* = 8.3, 7.3 Hz, 2H), 3.91 (d, *J* = 23.1 Hz, 1H), 3.72 (d, *J* = 23.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.1 (C), 146.5 (C), 143.1 (C), 142.8 (C), 140.9 (C), 138.9 (C), 136.7 (C), 135.8 (C), 134.9 (C), 133.6 (C), 132.2 (CH), 131.5 (C), 131.0 (CH), 130.6 (CH), 129.9 (CH), 128.0 (CH), 127.8 (CH), 127.8 (CH), 127.6 (CH), 126.6

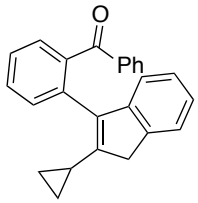
(CH), 126.2 (CH), 125.6 (CH), 125.6 (CH), 125.2 (CH), 125.1 (CH), 123.7 (CH), 120.5 (CH), 44.3 (CH_2); HRMS-ESI *m/z* calculated for $C_{32}H_{22}ONa$ $[M+Na]^+$ 445.1568, found 445.1561.

(2-(2-Benzyl-1*H*-inden-3-yl)phenyl)(phenyl)methanone (11h)



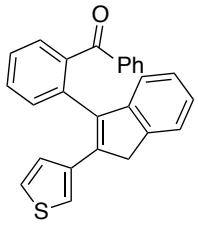
Indene **11h** was synthesized following the general procedure 3, starting from prop-2-yn-1-ylbenzene (9.34 mg, 0.08 mmol) and 1,3-diphenylisobenzofuran (43.5 mg, 0.16 mmol). The residue was purified by column chromatography (50:1 cyclohexane/EtOAc) to give compound **11h** (12.9 mg, 42%) as orange sticky solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (dd, J = 8.3, 1.4 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.65 (dd, J = 7.5, 1.4 Hz, 1H), 7.64 – 7.62 (m, 1H), 7.59 – 7.53 (m, 3H), 7.51 – 7.47 (m, 2H), 7.41 – 7.37 (m, 3H), 7.30 – 7.27 (m, 2H), 7.08 – 7.04 (m, 3H), 3.72 (d, J = 16.8 Hz, 1H), 3.37 (d, J = 15.1 Hz, 1H), 3.11 (d, J = 22.7 Hz, 1H), 2.79 (d, J = 22.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.5 (C), 145.2 (C), 142.4 (C), 140.3 (C), 139.9 (C), 138.9 (C), 137.8 (C), 137.7 (C), 132.4 (CH), 131.9 (CH), 131.1 (CH), 130.6 (CH), 130.2 (CH), 129.9 (CH), 129.6 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.5 (CH), 127.8 (CH), 127.2 (CH), 126.2 (CH), 124.42 (CH), 123.3 (CH), 120.1 (CH), 100.1 (C), 40.3 (CH_2), 35.7 (CH_2); HRMS-ESI *m/z* calculated for $C_{29}H_{22}ONa$ $[M+Na]^+$ 409.1568, found 409.1573.

(2-(2-Cyclopropyl-1*H*-inden-3-yl)phenyl)(phenyl)methanone (11i)



Indene **11i** was synthesized following the general procedure 3, starting from ethynylcyclopropane (7.81 mg, 0.12 mmol) and 1,3-diphenylisobenzofuran (63.9 mg, 0.24 mmol). The residue was purified by column chromatography (50:1 cyclohexane/EtOAc) to give compound **11i** (38.0 mg, 96%) as orange sticky solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.5, 1.5 Hz, 1H), 7.62 (dd, J = 7.5, 1.6 Hz, 1H), 7.57 – 7.40 (m, 4H), 7.21 – 7.10 (m, 3H), 7.08 – 6.92 (m, 4H), 2.85 (d, J = 22.1 Hz, 1H), 2.43 (d, J = 22.1 Hz, 1H), 1.66 (tt, J = 8.4, 5.1 Hz, 1H), 0.89 – 0.81 (m, 1H), 0.78 – 0.68 (m, 1H), 0.63 – 0.50 (m, 1H), 0.48 – 0.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.8 (C), 148.4 (C), 146.5 (C), 140.8 (C), 139.9 (C), 137.9 (C), 137.6 (C), 135.0 (C), 131.9 (CH), 131.0 (CH), 130.4 (CHH), 129.8 (CH), 129.0 (CH), 127.7 (CH), 127.5 (CH), 126.2 (CH), 123.8 (CH), 123.2 (CH), 118.9 (CH), 36.2 (CH2), 12.0 (CH_2), 8.8 (CH_2), 8.7 (CH_2); HRMS-ESI *m/z* calculated for $C_{25}H_{20}ONa$ $[M+Na]^+$ 359.1412, found 359.1418.

Phenyl(2-(2-(thiophen-3-yl)-1*H*-inden-3-yl)phenyl)methanone (11j)



Indene **11j** was synthesized following the general procedure 3, starting from 3-ethynylthiophene (11.0 mg, 0.10 mmol) and 1,3-diphenylisobenzofuran (55.0 mg, 0.20 mmol). The residue was purified by column chromatography (50:1 cyclohexane/EtOAc) to give compound **11j** (35 mg, 91%) as yellow

solid: mp 137-141 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.71 (m, 2H), 7.69 – 7.63 (m, 1H), 7.59 (dd, J = 7.5, 1.4 Hz, 1H), 7.56 – 7.53 (m, 1H), 7.38 (dd, J = 8.2, 1.5 Hz, 2H), 7.30 (d, J = 7.4 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.18 – 7.12 (m, 2H), 7.13 – 7.09 (m, 1H), 7.08 – 7.04 (m, 1H), 7.03 – 6.99 (m, 2H), 6.75 (dd, J = 5.0, 1.3 Hz, 1H), 3.61 (d, J = 22.2 Hz, 1H), 3.39 (d, J = 22.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.6 (C), 147.0 (C), 141.5 (C), 139.6 (C), 138.5 (C), 137.8 (C), 137.4 (C), 137.3 (C), 135.8 (C), 132.0 (CH), 131.5 (CH), 130.6 (CH), 130.3 (CH), 128.9 (CH), 128.0 (CH), 127.5 (CH), 127.0 (CH), 126.5 (CH), 125.3 (CH), 125.0 (CH), 123.3 (CH), 122.6 (CH), 120.4 (CH), 40.8 (CH_2); HRMS-ESI *m/z* calculated for $C_{26}H_{18}ONaS[M+Na]^+$ 401.0976, found 401.0967.