MECHANISTIC STUDIES ON GOLD MEDIATED CROSS-COUPLING REACTIONS AND TOTAL SYNTHESIS OF (_+)-EPIGLOBULOL

Madeleine Livendahl

Dipòsit Legal: T.1507-2013

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Mechanistic Studies on Gold Mediated Cross-Coupling Reactions and Total Synthesis of (±)-Epiglobulol

DOCTORAL THESIS

Supervised by Prof. Antonio M. Echavarren

Institut Català d'Investigació Química

UNIVERSITAT ROVIRA I VIRGILI
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FAIG CONSTAR que aquest treball, titulat "Mechanistic Studies on Gold Mediated Cross-Coupling Reactions and Total Synthesis of (±)-Epiglobulol", que presenta Madeleine Livendahl per a l'obtenció del títol de Doctor, ha estat realitzat sota la meva direcció al Departament de Química Analítica i Química Orgánica d'aquesta Universitat i que acompleix els requeriments per poder optar a Menció Europea.

Tarragona, 11 de Octubre de 2013

El Director de la Tesi Doctoral

Prof. Antonio M. Echavarren

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Till Henrik

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This Doctoral Thesis has been carried out in l'Institut Català d'Investigació Química under the supervision of Professor Antonio M. Echavarren to whom I am most grateful for giving me the opportunity to take part of his research group.

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Thanks to all the group members of the E-team I had the privilege to work with! Especial thanks to Dr. Paul McGonigal, Dr Juhanes Aydin and Dr. Riccardo Sinisi for all the help and guidance at work as well as all the good times we had. I also want to thank Mihai Raducan for teaching me all his tiquis-miquis giving me great skills with the inorganic chemistry! I wanna say a joint thanks to all the wonderful women of the group, thanks Nolwenn Martín, Ana Escribano-Cuesta, Núria Huguet, Claudia de Leon and Veronica Carillo (que viaje hemos cumplido juntas!) from the early times and thanks Morgane Gaydou (the sunshine of our lab!), Carla Obradors and Anna Homs for all great and releiving chats in the lab both on chemistry and all the rest! Tack Elina Buitrago för bästa tre månaderna!! Thanks to Dr. Ricarda Miller and Katya Smirnova for making the last three months truly memorable! Big thanks also to Yahui Wang for all the great help with "literature search" ;) Last but not least I would like to thank the two wonderful technicians I have worked with, gracias Vanessa Martínez y Imma Escofet, que lio tendríamos sin vuestra ayuda fantástica!

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

- Gold(I) Catalysis in Cross-Coupling Reactions

M. Livendahl, A. M. Echavarren, *Chim. oggi* **2012**, *30* (Suppl.), 19-21.

- Is Gold a Catalyst in Cross-Coupling Reactions in the Absence of Palladium?

M. Livendahl, P. Espinet, A. M. Echavarren, *Platinum Metals Rev.* **2011**, *55*, 212-214.

- Unlikeliness of Pd-Free Gold(I)-Catalyzed Sonogashira Coupling Reactions

T. Lauterbach, M. Livendahl, A. Rosellón, P. Espinet, A. M. Echavarren, *Org. Lett.* **2010**, *12*(13), 3006-3009.

(Awarded in 2010 as one of the ten most accessed articles of the journal)

Other publications not related to the topics covered in this manuscript are presented below:

- Palladium-Catalyzed Arylation Reactions: A Mechanistic Perspective

M. Livendahl, A. M. Echavarren, *Isr. J. of Chem.* **2010**, 630-651.

This thesis has been done in two parts. The first two chapters have been prepared at the Institute of Chemical Research of Catalonia under the supervision of professor Antonio M. Echavarren and the third chapter at Novartis Institutes of Biomedical Research under the supervision of Dr. Laure Bouchez.

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Abbreviations and Acronyms

In this manuscript, abbreviations and acronyms have been used, according to the "guidelines for authors" of *The Journal of Organic Chemistry*.

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

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

conv	conversion
N. R.	no reaction
BAr_F	tetrakis[(3,5-trifluoromethyl)phenyl]borate
Johnphos	(2-Biphenyl)di-*tert*-butylphosphine
Dppe	1,2-Bis(diphenylphosphino)ethane
NHC	*N*-heterocyclic

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Resumen de la Tesis

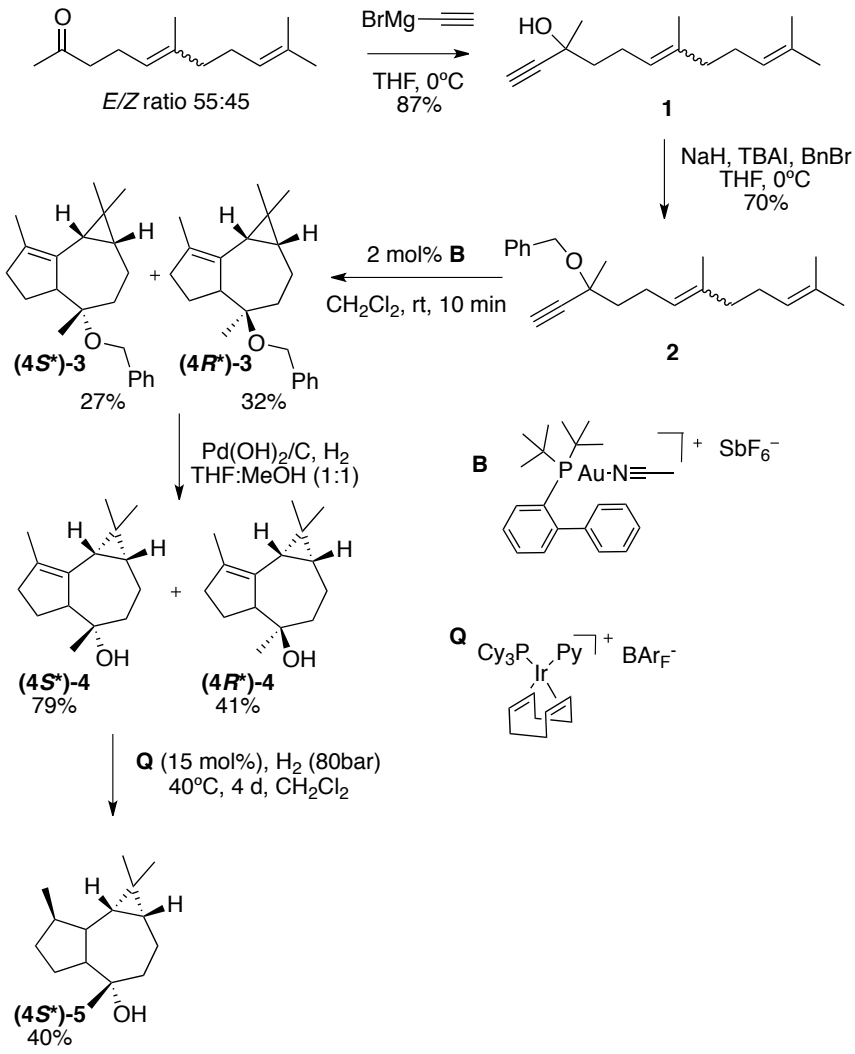
Capitulo uno – Sintesis total de (±)-epiglobulol

La catálisis de oro se ha diversificado de una manera exponencial durante los últimos 20 años. Un metal que anteriormente había sido considerado inútil en catálisis, ahora es uno de los metales mas importantes como el paladio o rodio.[1] La catálisis de oro procede en condiciones suave y normalmente con cantidades muy pequeñas de catalizador.[2] Además, ha mostrado una diversidad muy grande, dando lugar a productos muy complicados en una sola transformación.[3]

Tras la activación con complejos catiónicos de oro(I), los 1,6-eninos conteniendo alcoholes o éteres proceden via una migración 1,5 dando lugar a cationes de alil-oro. Estos intermedios se pueden atrapar intra- o intermolecularmente con alquenos o éteres bencílicos.[4] Esta reacción estereospecífica da lugar a compuestos tricíclicos relacionados con los sesquiterpenos 4-epiglobulol y 4-aromadendreno. La síntesis racémica del 4-epiglobulol se comenzó a partir del geranyl acetona que es comercial (esquema 1). En dos pasos se obtuvo el intermedio dienino (**2**) con un rendimiento total 61%. El dienino **II** fue ciclado empleando el catalizador de oro(I) **B**, obteniéndose los dos epímeros del cicloaducto **3** en un rendimiento total de 58%. La desprotección del éter bencílico se realizó empleando hidróxido de paladio sobre carbón activo bajo la presión de un bar de hidrogeno con un rendimiento cuantitativo. El doble enlace en el epímero (4*S*) del cicloaducto **4** se ha reducido bajo 80 bares de atmosfera de

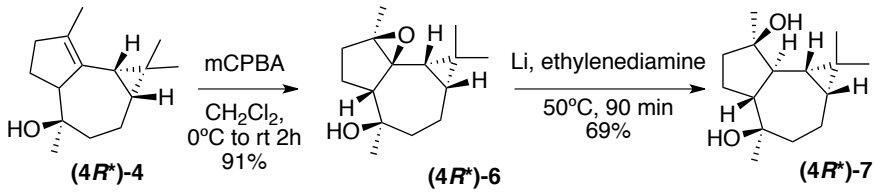
[1] (a) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766-1775. (b) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448-2462.
[2] (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2302-2406. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677-1693.
[3] For examples see following reviews: (a) Brenzovich, W. E. *Angew. Chem Int. Ed.* **2012**, *51*, 8933-8935. (b) Alcaide, B.; Almendros, P.; Alonso, J. M. *Molecules* **2011**, *16*, 7815-7843. Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239-3265.
[4] Jiménez-Núñez, E.; Raducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren A. M. *Angew. Chem. Int. Ed.* **2009**, *48* , 6152-6155.

hidrogeno durante 4 días a 40ºC empleando el catalizador **Q** de Crabtree con BAr_F como contra-anión. La reacción ha dado el producto natural, (±)-4-epiglobulol, con un rendimiento de 40% (rendimiento total de 16%).



Esquema 1. Sintesis total de (±)-epiglobulol.

Desde el epímero (*R*) del cicloaducto **4** se ha sintetizado en dos pasos adicionales el producto natural (±)-aromadendranediol con un rendimiento total de 11% (esquema 2).[5]



Esquema 2. Sintesis total de (±)-aromadendranediol.

Con la intención de realizar la síntesis de productos naturales halichonadin E y F (figura 1), que tienen una estructura relacionada con el epi-globulol y el aromadendranediol, hemos sintetizado un grupo pequeño de eninos y dieninos con una amina propargilica en lugar de un éter o un alcohol (esquema 3).

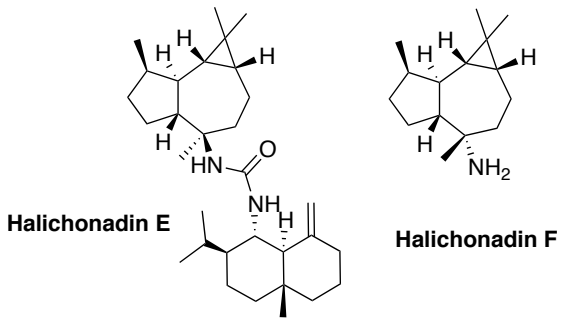
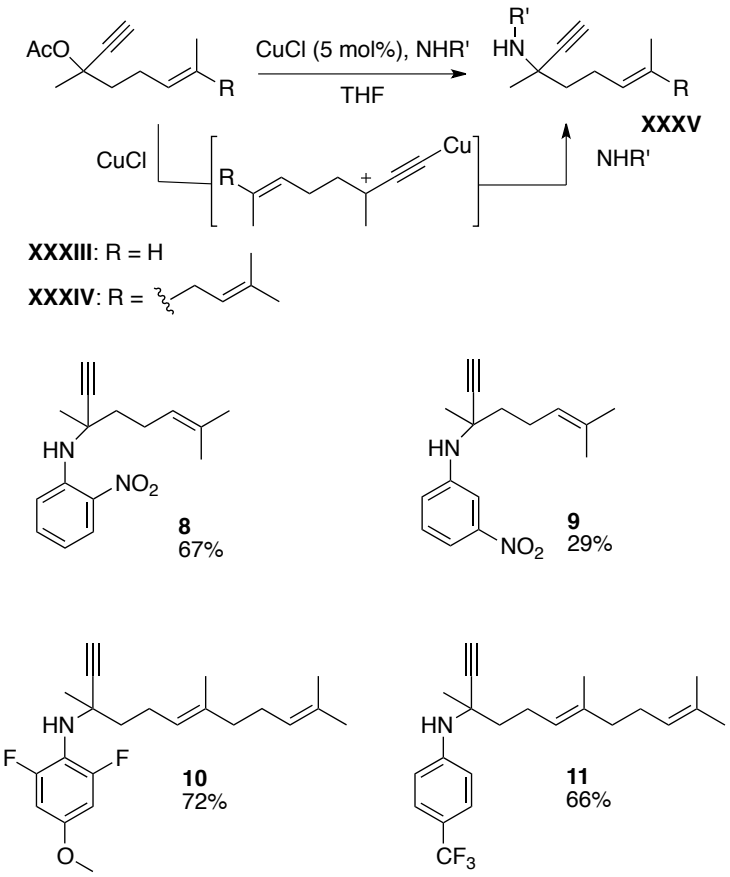


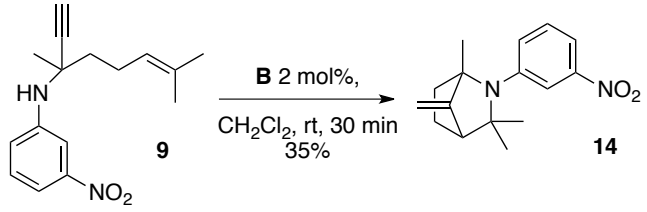
Figura 1. Compuestos naturales halichonadin E y F.

Desafortunadamente, solo uno de estos eninos ha ciclado con las condiciones previamente optimizadas (esquema 4).

[5] Resultados sin publicar en colaboración con Dr. Paul R. McGonigal.



*Esquema 3. Síntesis de aminas propargílicas (**8-11**)*



*Esquema 4. Ciclación del enino **9** catalizada por el complejo **B**.*

Capitulo dos – Estudios mechanisticos de reacciones de acoplamiento C-C mediado de oro.

Una de las reacciones más investigadas en el mundo de la química hasta hoy es el acoplamiento C-C. El desarrollo del acoplamiento C-C catalizado con un metal transición empezó en los años 60 con Heck[6] seguido de Suzuki, [7] Negishi, [8] Sonogashira [9] y Stille. [10] Este método cambió por completo la química y Heck, Suzuki y Negishi fueron reconocidos por su trabajo con el premio Nobel en 2010.[11] El oro también ha entrado en el mundo de catálisis de acoplamientos C-C, por ejemplo acoplamiento oxidativos y cooperando con otro metal de transición desarrollados por varios grupos de investigación.[12] También salieron algunos artículos de investigación mostrando la capacidad del oro de catalizar en reacciones tradicionalmente catalizadas por paladio.[13] El argumento fue cómo tanto que el oro(I) como el paladio(0) tienen una configuración electrónica d^{10} deberían presentar la misma reactividad en estas reacciones. Sin embargo, este argumento nos pareció demasiado simplificado para una reactividad tan complicada. Por ejemplo, hay varias diferencias entre la catálisis del paladio(0) y el platino(I) aunque el platino también, como el paladio y el

[6] Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518-5526. (b) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5526-5531. (c) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5531-5534. (d) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5538-5542. (e) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5542-5546.

[7] (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437-3440. (b) Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun.* **1979**, *19*, 866-867.

[8] (a) Negishi, E.-I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821-1823. (b) King. A. O.; Okukado, N.; Negishi, E.-I. *Chem. Commun.* **1977**, *19*, 683-684.

[9] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467-4470.

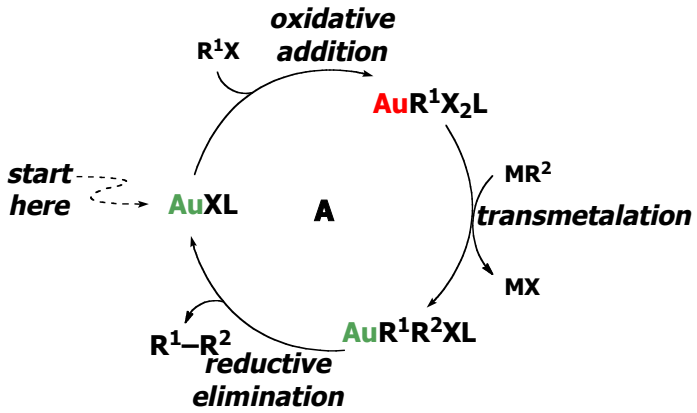
[10] Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992-4998.

[11] "The Nobel Prize in Chemistry 2010 - Press Release". Nobelprize.org. 13 Apr 2013
http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/press.html

[12] (a) Hashmi, A. S. K.; Lothschütz, Döpp, R.; Rudolph, M.; Ramamurthi, T. D.; Rominger, F. *Angew. Chem. Int. Ed.* **2009**, *48*, 8243-8246. (b) Hashmi, A. S. K.; Ghanbari, M.; Rudolph, M.; Rominger F. *Chem. Eur. J.* **2012**, *18*, 8113-8119. (c) Shi, Y.; Roth, K. E.; Ramgren, S. D.; Blum, S. A. *J. Am. Chem. Soc.* **2009**, *131*, 18022-18023. (d) Shi, Y.; Peterson, S. M.; Haberaecker, W. W.; Blum, S. A. *J. Am. Chem. Soc.* **2008**, *130*, 2168-2169.

[13] Plenio, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 6954-6956.

oro, tiene configuración d[10].[14] Para investigar la naturaleza de la reactividad del oro en un ciclo catalítico de un acoplamiento C-C hemos estudiado dos propuestas posibles. El ciclo clásico en una reacción catalizada por paladio empieza con una adición oxidante cambiando el estado de oxidación del metal seguida de una transmetalación dando lugar a un intermedio metálico coordinado a dos carbonos. Estos dos sustituyentes se acoplan en una eliminación reductiva liberando oro con el mismo estado de oxidación que al principio (esquema 5). Sin embargo, el oro también puede entrar en el ciclo catalítico desde la transmetalación, seguido de una adición oxidante como en el ciclo anterior y los dos sustituyentes coordinados con el oro acoplandose en una eliminación reductiva.

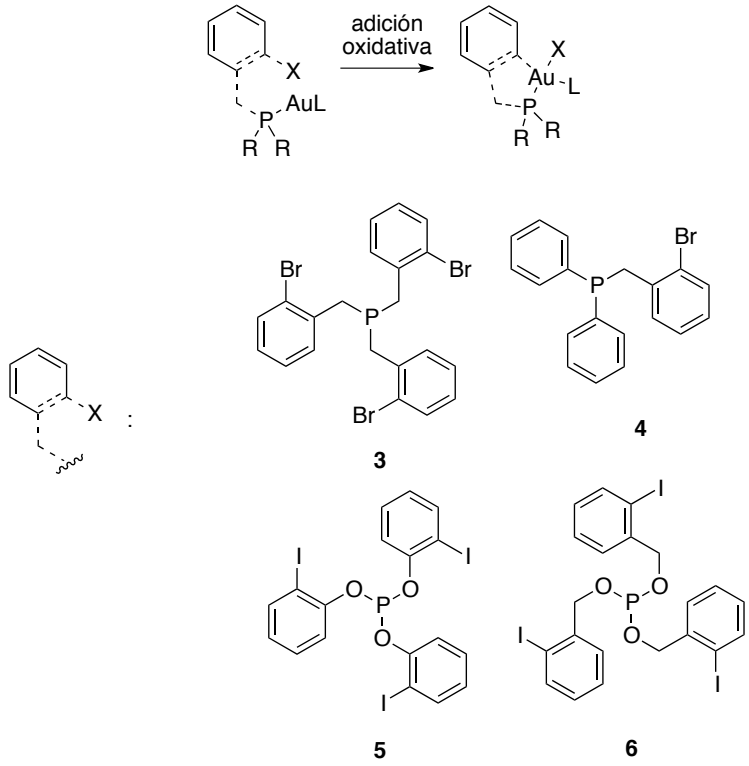


Esquema 5. Ciclo catalítico de acoplamiento C-C mediado de oro.

Hemos investigado todos los pasos de los dos ciclos demonstrando que el paso retrasando en los dos ciclos es la adición oxidante. Es conocido que el oro tiene una resistencia intrínseca a cambios de su estado de oxidación. Junto con el grupo de Profesor Maseras hemos realizado cálculos de una reacción de acoplamiento C-C catalizada por oro igual como las reacciones del paladio. Los resultados muestran barreras de energía para los estados de

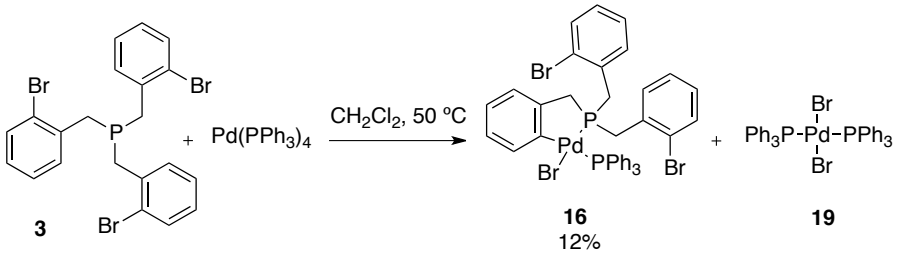
[14] (a) Mateo, C.; Fernández-Rivas, C.; Cárdenas, D. J.; Echavarren, A. M. *Organometallics* **1998**, *17*, 3661–3669. (b) Nilsson, P.; Puxty, G.; Wendt, O. F. *Organometallics* **2006**, *25*, 1285–1292.

transición de 40 kcal/mol lo cual prohíbe la reacción en las condiciones normales para una reacción catalítica de este tipo. Para intentar diseñar una reacción donde la adición oxidante sea muy favorable hemos sintetizado ligandos para el metal que tienen incorporado un arilo substituido con un haluro, que en principio podría añadirse oxidante al metal formando ciclos de cinco o seis miembros (esquema 6).



*Esquema 6. Diseño de ligandos nuevos (**4-6**) con un arilo substituido con un haluro.*

Hemos coordinado los cuatro ligandos al oro(I) y hemos intentado provocar la adición oxidante de varias maneras. Sin embargo, no hemos obtenido los productos cíclicos en ninguno de los casos. Para confirmar la reactividad del ligando **3**, lo hemos coordinado a paladio y hemos obtenido el producto de la adición oxidante (esquema 7).



*Esquema 7. Coordinación del ligando **3** a paladio.*

El grupo del Profesor Maseras han calculado también las barreras del estado transición con el sistema de la adición oxidante intramolecular y han obtenido resultados iguales a los obtenidos previamente. Parece que la adición oxidante en un sistema intramolecular tiene un estado de transición muy alto a causa de la relación *trans* entre el haluro y el arilo que se añade. Esta relación hace que la reacción sea entrópicamente igual de desfavorable que en el sistema intermolecular.

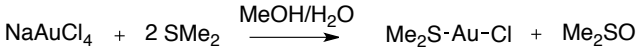
Introduction

In recent years the Au(I)-catalyzed activation of alkynes towards nucleophilic attack has found a significant place in syntheses of natural compounds. This high affinity towards unsaturation is thought to be due to the high Lewis acidity of cationic Au(I) together with its ability to stabilize cationic reaction intermediates. To understand this reactivity of gold, it is necessary to look into its relativistic effects. These relativistic effects become important in atoms where the electron is strongly attracted to a heavy nucleus by electrostatic effects where they cause the electron to adopt a near to light speed.[1] A consequence of this is the proportional increase of the mass of the electron and the subsequent contraction of the s and p orbitals. This contraction is especially pronounced within metals that have filled 4f and 5d orbitals, such as Pt, Au and Hg. In Au the atomic radius reaches a local minimum, effectively causing a strong contraction of the 6s orbital shell, which might explain its strong electronegativity and strong Lewis acidity. Together with this radial contraction of the 6s shell there is a concomitant expansion and destabilization of the 5d shell. The effect of this is a contraction of the Au-L bond, the strength of which is sensitive to the type of L. This gives a natural window of opportunity to alter the electronic nature of the resulting complex by fine-tuning electronic, as well as steric, properties of the ligand, L.

Simple gold salts such as AuCl, $AuCl_3$ and $NaAuCl_4$ are carbophilic enough for the activation of alkynes towards nucleophilic attack. However, Au(III) is easily reduced to Au(I) and Au(0) by oxidizable substrates. Conversely Au(I) complexes with stabilizing donor ligands can disproportionate to Au(0) and Au(III) in some cases.[2] Au(I) complexes have a strong

[1] (a) Gimeno, C. (2008). *The Chemistry of Gold*. Weinheim:Wiley. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395-403. (c) Schmidbaur, H. Pyykkö, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 3573-3578. (d) Schmidbaur, H; Cronje, S.; Djordjevic, B.; Schuster, O. *Chem. Phys.* **2005**, 151-161.
[2] Jiménez-Núñez, E; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326-3350.

preference to form two-coordinate, linear complexes. This is due to the short bond distances to gold, which affects the hybridization of the orbitals. The syntheses of this type of complexes are usually trivial. The facile reduction of an inexpensive Au(III)-chloride salt by thiols or thioethers such as 1,2-ethane dithiol, dimethyl sulfide or thiophene in the presence of water gives a Au(I) chloride complex bearing a labile sulfur ligand (Scheme 1. 1).[3]



Scheme 1. 1. Formation of gold-chloro complexes bearing a labile thiol ligand.

This labile sulfur ligand can easily be displaced by a ligand of choice (L) to gain access to the corresponding Au(I)-chloro complex. Further activation for catalysis is often required and is done by substitution of the chloride by a weaker ligand. This can be done by one equivalent of a Ag(I) salt with a non-coordinative anion in the presence of a labile ligand, often acetonitrile or benzonitrile. The reaction can either be performed *in situ*, or isolated as stable crystalline solids. Our group has designed and developed several of the commercially available cationic Au complexes that are frequently used for Au mediated catalysis.[4] Recently it was found that copper salts could also be used for the *in situ* removal of halides bore by the gold in catalysis.[5]

The electrophilicity of Au(I) complexes is strongly influenced by the choice of its ligands. This is clear when comparing results from reactions catalyzed

[3] (a) Dash, K. C.; Schmidbaur, H. *Chem. Ber.* **1973**, *106*, 1221-1225. (b) Uson, R.; Laguna, A.; Laguna, M. *Inorg. Synth.* **1989**, *26*, 85-91.
[4] (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2302-2406. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677-1693.
[5] Guérinot, A.; Fang, W.; Sircoglou, M.; Bour, C.; Bezzenine-Lafollée, S.; Gandon, V. *Angew. Chem. Int. Ed.* **2013**, *52*, 5848-5852.

by gold complexes ligated to *N*-heterocyclic carbenes (NHCs), with other gold complexes bearing phosphines or phosphites as ligands (Figure 1. 1).

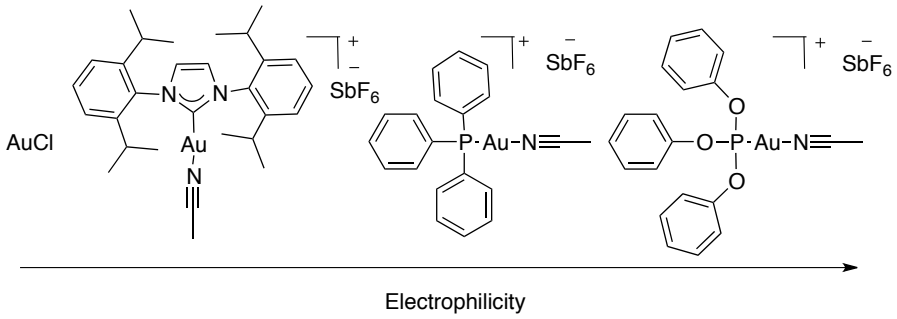


Figure 1. 1. Electronegativity scale of different cationic gold complexes.

The high donation of electron density from the NHC ligand towards the gold atom has rendered this class of catalysts very selective.[6,7] A more electrophilic complex can be accessed when L is a phosphine instead. The first examples in catalysis using phosphine Au(I) complexes were reported by the group of Teles.[8] Phosphine gold complexes in catalysis has since

[6] a) de Frémont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 2411-2418. b) de Frémont, P.; Stevens, E. D.; Fructos, M. R.; Diaz-Requejo, M. M.; Perez, P. J.; Nolan, S. P. *Chem. Comm.* **2006**, *19*, 2045-2047. c) López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029-6032. d) Liu, X.-Y.; Ding, P.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2007**, *9*, 2645-2648.

[7] Clavier, H.; Nolan, S. P. *Chem. Comm.* **2010**, *46*, 841-861.

[8] Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.

then been widely diversified.[9] Selected examples of gold catalysts and precatalysts are shown in figure 1. 2.[4,6c,8,10,11]

[9] (a) Arcadi, A.; Di Guiseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795-812. (b) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387-391. (c) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, *20*, 4555-4563. (d) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7896-7936. (e) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, *4*, 333-346. (f) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180-3211. (g) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449.

[10] (a) Giner, X.; Nájera, C. *Org. Lett.* **2008**, *10*, 2919-2922. (b) Álvarez, E.; Miguel, D.; García-García, P.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Beilstein J. Org. Chem.* **2011**, *7*, 786-793.

[11] González, A. Z.; Toste, F. D. *Org. Lett.* **2009**, *12*, 200-203.

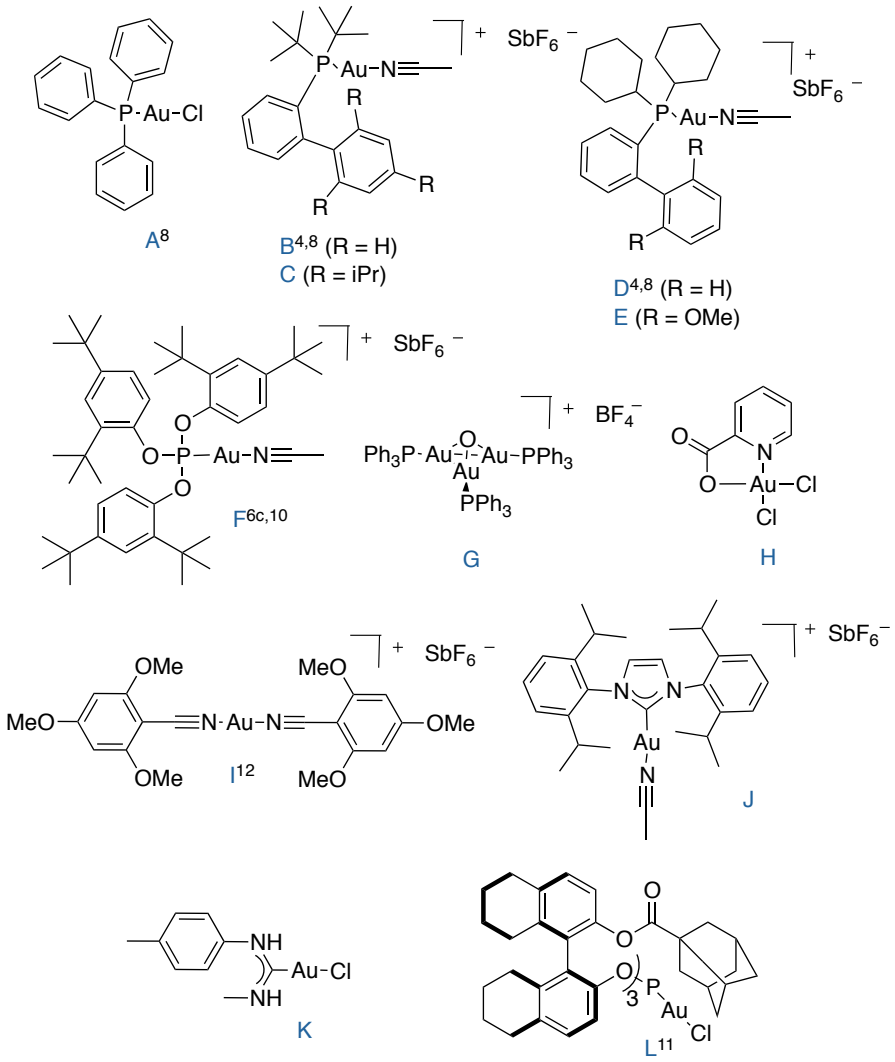


Figure 1. 2. Examples of gold complexes.

Inspired by Pd catalysis, where a precatalyst can be mixed *in situ* with the desired ligand to form the active catalytic complex, without previous isolation, there has also been a demand for an equivalent Au precatalysts. In our group, we developed a gold(I)-bis-2,4,6-trimethoxy-benzonitrile cationic complex with SbF_6 as counterion (complex **I**, figure 1. 2).[12] The

[12] Raducan, M; Rodríguez-Escrich, C; Cambeiro, X. C.; Escudero-Adán, E. C.; Pericàs, M. A.; Echavarren, A. M. *Chem. Commun.* **2011**, *47*, 4893-4895.

precatalyst is air and light stable and in solution in the presence of a ligand (L) of choice forms the active cationic [L-Au-(2,4,6-trimethoxy-benzonitrile)]$^{+}$ complex.

Au(III) complexes such as **H** have also been used in catalysis.[13] It has also been argued that asymmetric catalysis could be more easily accessible through the use of Au(III) catalysts due to its square planar structure.[14] Au(III) complexes can be obtained by oxidation of Au(I) complexes in the presence of Br_2 or Cl_2-gas.[15]

There are four orbitals that are able to participate when an alkyne acts as a ligand towards gold. The in-plane orbitals π_{II} and the π_{II}^{*} are responsible for a σ-donor interaction (M←L donation) and a π acceptor interaction (M→L back donation) respectively. The orthogonal out-of-plane orbitals π and π* participate in the M←L π donation and the delta symmetry M→L back donation respectively. Due to weak overlap of the orbitals the latter can be neglected. Alkynes are strong σ donors and have a weaker π interaction towards gold, which, according to the Dewar-Chatt-Duncanson model,[16] results in an elongation of the triple bond due to the net change of electrons from the π to the π* orbital, thus making the triple bond susceptible for nucleophilic attack.

[13] Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovi, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545-6547.
[14] Sengupta, S.; Xiaodong, S. *Chem. Cat. Chem*. **2010**, *2*, 609-619.
[15] de Frémont, P.; Sing, R.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2007**, *26*, 1376-1385.
[16] (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.

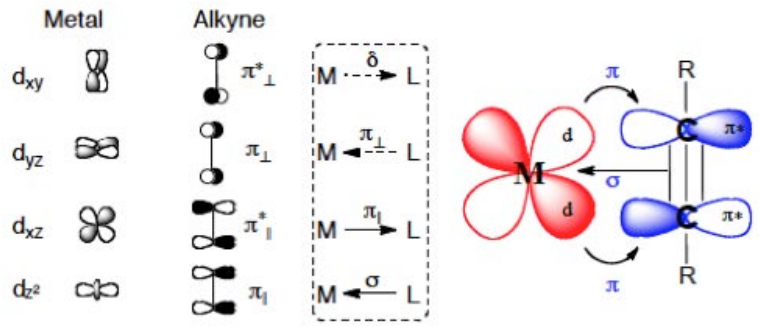
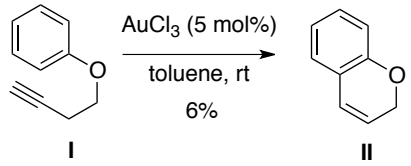


Figure 1. 3. Qualitative orbital model.

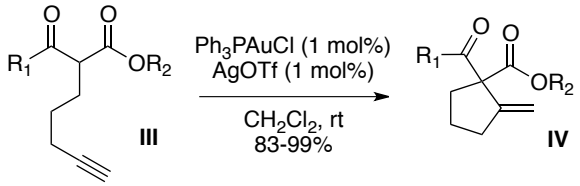
Nucleophilic attack of simple alcohols water to alkynes, allenes and olefins, were one of the first gold catalyzed reactions to be discovered under homogeneous conditions.[17] Sulfur[18] and nitrogen[19] nucleophiles were also investigated. Particular emphasis was placed on the finding of the addition of carbon nucleophiles in the gold-catalyzed hydrofunctionalization of C-C multiple bonds. A first example was the use of $AuCl_3$ as catalyst for the Friedel-Crafts reaction of propargyl phenyl ethers (**I**) resulting in bicyclic products **II** in very low yield (scheme 1. 2).[20]

[17] (a) Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. Soc. Perkin Trans. 1* **1976**, 1983-1987. (b) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729-3731. (c) Fukuda, Y.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013-2015.
[18] Morita, N.; Krause, N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1897-1899.
[19] (a) Fukuda, Y.; Utimoto, K. *Synthesis* **1991**, 975-978. (b) Müller, T. E. *Tetrahedron Lett.* **1998**, *39*, 5961-5962. (c) Müller, T. E.; Grosche, M.; Herdtweck, E.; Pleier, A.-K.; Walter, E.; Yan, Y.-K. *Organometallics* **2000**, *19*, 170-183. (d) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349-3352. (e) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260-11261.
[20] Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055-1058.



Scheme 1. 2. Cyclization of propargyl phenyl ethers.

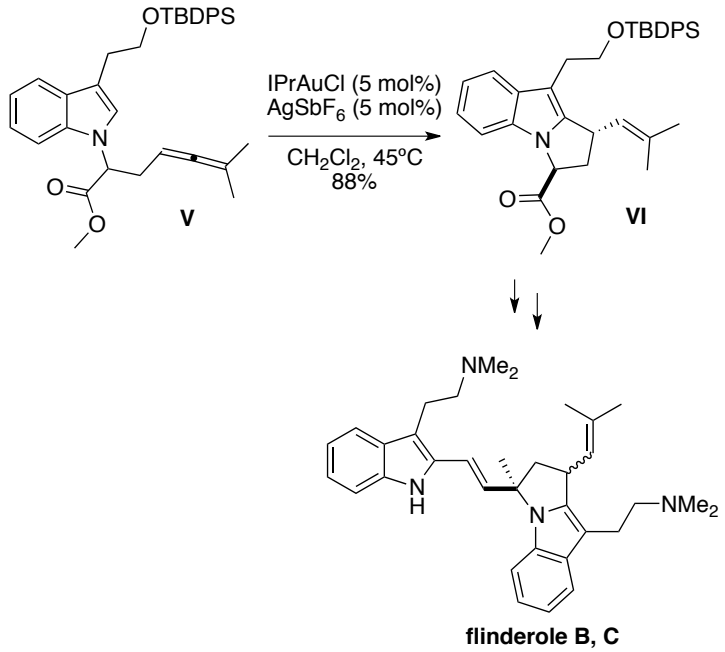
Toste [21] later reported the intramolecular Conia-ene reaction with a nonsubstituted alkyne **III** for the formation of carbocyclic compounds **IV** under mild conditions (scheme 1. 3).



Scheme 1. 3. Conia-ene reaction.

Around that time Arcadi and co-workers [22] also found the successful coupling of α,β unsaturated ketones with indoles catalyzed by gold salts under mild conditions. A related hydroheteroarylation reaction was later applied in the total synthesis of potential anti-malarial compounds, flinderole B and C (scheme 1. 4).[23] The indole-substituted allene gives the 5-exo-*trig* cyclization product **VI** as a single diastereoisomer in 88% yield. The key intermediate was then further functionalized in a total of 18 steps giving flinderole B and C in a 4 % overall yield.

[21] Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526-4527.
[22] Arcadi, A.; Bianchi, G.; Chiarini, M.; D'Anniballe, G.; Marinelli, F. *Synlett* **2004**, 944-950.
[23] (a) Zeldin R. M.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1706-1709. (b) Fernandez, L. S.; Buchanan, M. S.; Carroll, A. R.; Feng, Y. J.; Quinn R. J.; Avery, V. M. *Org. Lett.* **2008**, *11*, 329-332

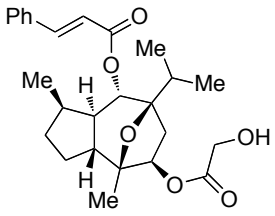


Scheme 1. 4. Gold catalyzed step in the total synthesis of flinderole B and C.

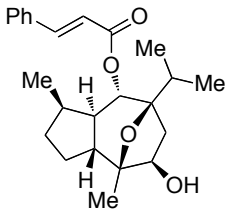
The discovery of inter- and intramolecular addition of carbon nucleophiles to C-C multiple bonds catalyzed by gold has been diversified in our group by the investigation of cyclization of enynes of different designs and chain lengths.[2] As an example the cyclization of 1,6-enynes by formal [2+2+2] alkyne/alkene/carbonyl cycloaddition [24] has resulted in the designed syntheses of pubinernoid B, orientalol F[25] and englerin A,[26] all based on the same tricyclic core bearing an oxo-bridge. Englerin A and B were synthesized simultaneously and were later investigated for their anti-carcinogenic properties, as it had been found earlier that extracts containing

[24] Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5422-5455.
[25] Jiménez-Núñez, E.; Molawi, K., Echavarren, A. M. *Chem. Commun.* **2009**, *47*, 7327-7329.
[26] Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3517-3519. See also the back-to-back paper by Ma for a complementary route; Zhou, Q.; Qianghui, C.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 3513-3516.

the two compounds from the plant *Phyllantus engleri* had selective potency against renal tumor cells.[27]

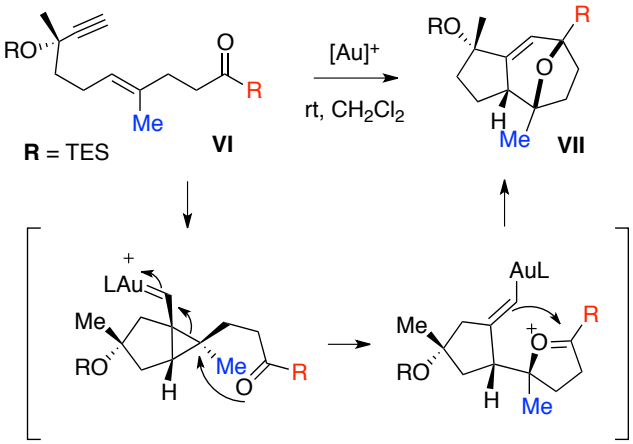


(-)-Englerin A



(-)-Englerin B

The key step in the above mentioned syntheses of orientalol F and englerin A is the Au(I) mediated stereoselective cyclization step of ketoenynes (**VI**) into oxatricycles (**VII**), presumably through a cyclopropyl gold carbene and vinyl gold intermediates (scheme 1. 5).



Scheme 1. 5. Cycloisomerization of 1,6-keto-enynes catalyzed by gold.

[27] (a) Ratnayake, R.; Covell, D.; Ransom, T. T.; Gustafson, K. R.; Beutler, J. A. *Org. Lett.* **2008**, *11*, 57-60. (b) Sourbier, C.; Scroggins, B. T.; Ratnayake, R.; Prince, T. L.; Lee, S.; Lee, M.-J.; Literati Nagy, P.; Lee, Y. H.; Trepel, J. B.; Beutler, J. A.; Linehan, W. M.; Neckers, L. *Cancer Cell* **2013**, *23*, 228-237.

Two different modes of activation of alkynes have been observed with gold; (1) π-complexation, promoting the nucleophilic attack to form *trans*-alkenyl-gold complexes as intermediates, (2) σ-acetylide complexes formed through exchange with the acidic terminal proton of the alkyne (figure 1. 4). These σ-acetylide complexes can form gem-σ-σ-diaurated species formally through a three center 2-electron bond.[28] In addition, dual σ-π activation has been observed in some gold catalyzed reactions.[29] The formation of these complexes has been seen to slow down intermolecular cyclization reactions between alkynes and furans and in intermolecular reactions of oxoalkenes with alkynes.[30] Addition of acid to the reaction mixture was shown to be beneficial, supposedly through the displacement of the σ bound gold center.

Our group recently found that the cationic (*t*Bu-XPhos)gold(I)-acetonitrile complex bearing BAr_F as counteranion also reduces the amount of the σ-π di-gold species. However, the mechanism for how this occurs is still under investigation.[31]

[28] (a) Gómez-Suárez, A.; Dupuy, S.; Slawin, A. M.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2013**, *52*, 938-942. (b) Zhadanko, A.; Maier, M. E. *Organometallics* **2013**, *32*, 2000-2006. (c) Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, D. E. *J. Am. Chem. Soc.* **2008**, *130*, 4517-4526.
[29] Brown, T. J.; Widenhoefer, R. A. *Organometallics* **2011**, *30*, 6003-6009.
[30] (a) Huguet, N.; Leboeuf, D.; Echavarren, A. M. *Chem. Eur. J.* **2013**, *19*, 6581-6585. (b) Obradors, C., Echavarren, A. M. *Chem. Eur. J.* **2013**, **19**, 3547-3551.
[31] C. Obradors, A. Homs, D. Leboeuf, unpublished results, ICIQ, 2013.

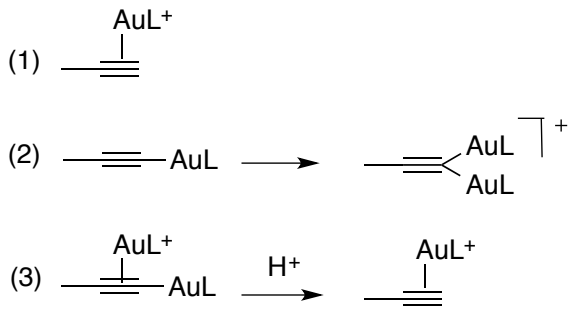
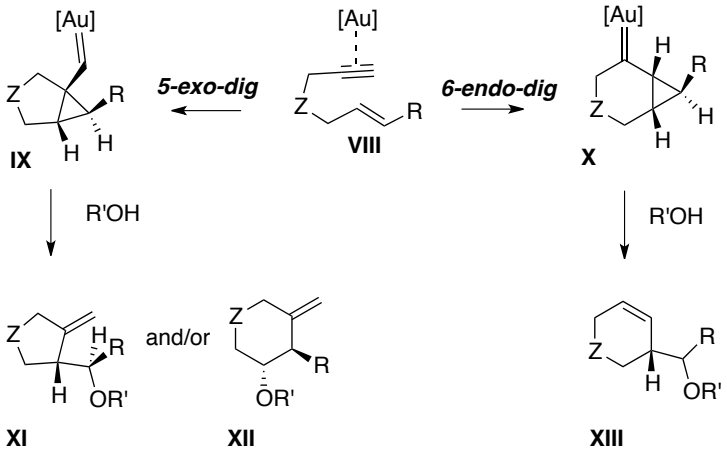


Figure 1. 4. Activation modes for gold on alkynes.

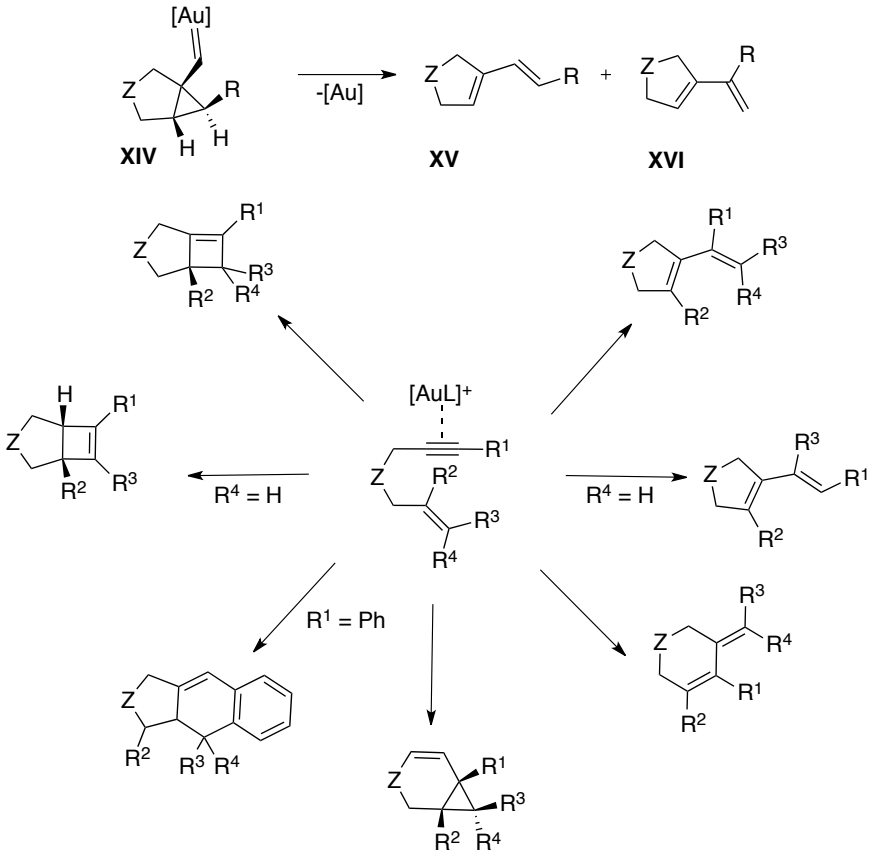
In the cyclization reactions of 1,6-enynes the mode of activation is the π-activation of the triple bond promoting the nucleophilic attack from the internal alkene. This attack occurs in an anti fashion with regards to the gold atom in a 5-*exo*-dig or 6-*endo*-dig pathway (scheme 1. 6).



Scheme 1. 6. Cyclization reaction of 1,6-enynes catalyzed by gold in the presence of nucleophiles

The exo/endo selectivity depends on the nature of the catalyst as well as the substitution pattern of the enyne. In the absence of nucleophiles cycloisomerization of 1,6-enynes can produce a large variety of products

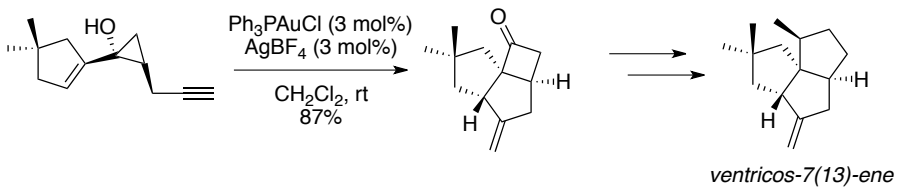
(scheme 1. 7). The mechanism goes through either single cleavage, giving dienes (**XV**), or double cleavage, giving dienes (**XVI**).[32]



Scheme 1. 7. Intramolecular cyclization reaction of 1,6-enynes catalyzed by gold in the absence of nucleophiles.

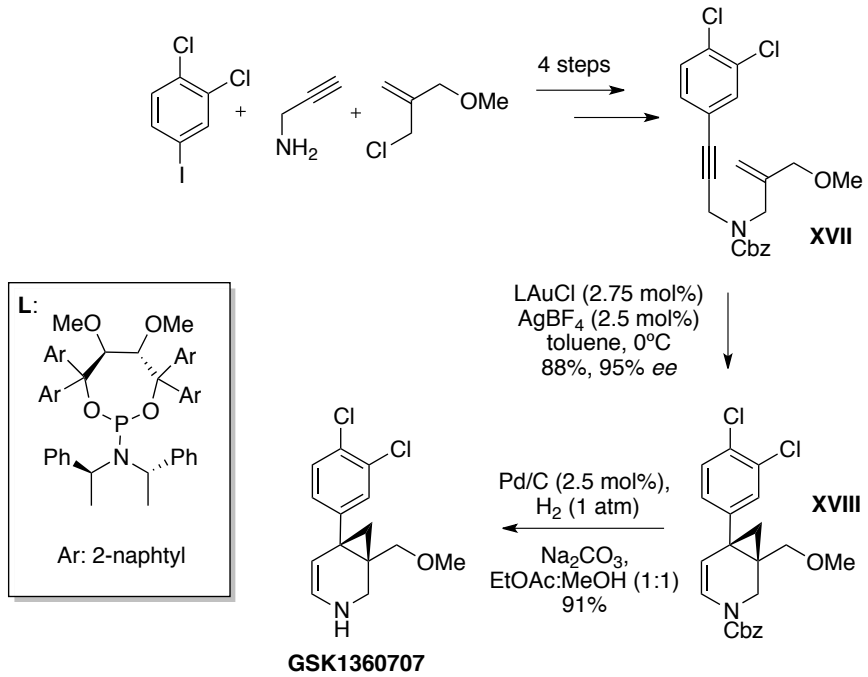
Cyclization of 1,6-enynes catalyzed by gold has been applied in total synthesis applications by, among others, the group of Toste[33] for the synthesis of the natural compound Ventricosene (scheme 1. 8).

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



Scheme 1. 8. Total synthesis of Ventricosene.

Another interesting example of gold catalysis applied in a total synthesis was made by Fürstner and Teller for the synthesis of GSK1360707.[34] They utilized an enantioselective enyne cyclization reaction, catalyzed by a chiral phosphoramidite gold catalyst. The synthesis was remarkably efficient giving the desired product in 6 steps (scheme 1. 9).



Scheme 1. 9. Total synthesis of GSK1360707.

[33] Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, D. F. *Org. Lett.* **2008**, *10*, 4315-4318.

[34] Teller, H; Fürstner, A. *Chem. Eur. J.* **2011**, *17*, 7764-7767.

Many other examples of gold catalysis being applied in total synthesis exist[35] and show the large complexity that can be created with high selectivity and efficiency.

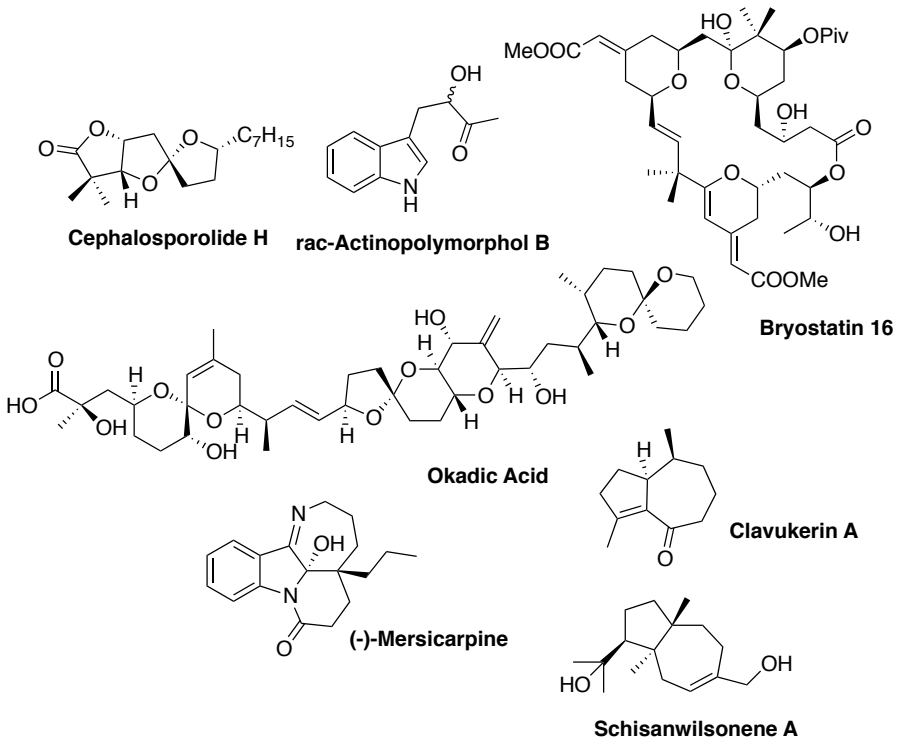


Figure 1. 5. Examples of natural products with syntheses involving a gold-catalyzed step.

[35] For examples see following reviews: (a) Brenzovich, W. E. *Angew. Chem Int. Ed.* **2012**, *51*, 8933-8935. (b) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766-1775. (c) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448-2462. (d) Alcaide, B.; Almendros, P.; Alonso, J. M. *Molecules* **2011**, *16*, 7815-7843. Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239-3265. (e) Gaydou, M.; Miller, R. E.; Delpont, N.; Ceccon, J. Echavarren, A. M. *Angew. Chem. Int. Ed.* **2013**, 52, 6396-6399.

Total Synthesis of (±)-Epiglobulol

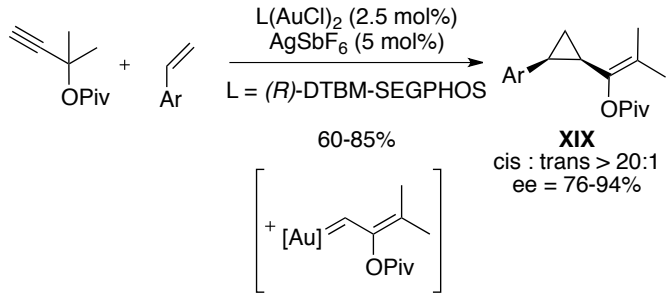
Introduction

1,6-Enynes bearing carbonyl groups cycloisomerize in the presence of gold catalysts forming oxo-bridged products, resulting from the intramolecular nucleophilic attack of the carbonyl oxygen. This gave accessibility to carbo-skeletons resembling the natural products orientalol F and englerins A and B (scheme 1. 5). The stereoinduction of the resulting oxo-bridge is controlled by the geometry of the internal double bond, and the configuration of one of the carbons in the ring junction is controlled by the configuration at the propargylic carbon.

1,6-Enynes bearing propargylic esters were found to undergo 1,2- and 1,3-acyloxy migration catalyzed by transition metals such as Zn,[36] Pt,[37] Rh,[38] Ru,[39] Au[40] and Pd.[41] The outcome of the reaction can be tuned by altering the metal, the ligand or substitution patterns of the reacting intermediates. The selectivity for the 1,3-acyloxy shift versus the 1,2-acyloxy shift is not well known but has been suggested to be interchangeable intermediates in a gold activation cycle.[42] In general terms, selectivity for 1,2-acyloxy migration can be achieved when using enynes bearing terminal alkynes. For substituted alkynes, the 1,3-migration was seen to dominate.[43]

[36] Strickler, H.; Davis, J. B.; Ohloff, G. *Helv. Chim. Acta* **1976**, *59*, 1328-1332.
[37] (a) Zheng, H.; Zheng, J.; Yu, B.; Chen, Q.; Wang, X.; He, Y.; Yang Z.; She, X. *J. Am. Chem. Soc.* **2010**, *132*, 1788-1789. (b) Zhang, G.; Catalano, V. J.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 11358-11359.
[38] Shu, X.-Z.; Shu, D.; Schienebeck, C.; Tang, W. *Chem. Soc. Rev.* **2012**, *41*, 7698-7711.
[39] Tenaglia, A.; Marc, S. *J. Org. Chem.* **2006**, *71*, 3569-3575.
[40] (a) Shiroodi, R. K.; Gevorgyan, V. *Chem. Soc. Rev.* **2012**, *42*, 4991-5001. (b) Leboef, D.; Simonneau, Aubert, C.; Malacria, M.; Gandon, V.; Fensterbank, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 6868-6871.
[41] Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950-952.
[42] Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 718-721.
[43] Marion, N.; Lemiere, G.; Correa, A.; Costabile, C.; Ramon, R. S.; Moreau, X.; de Fremont, P.; Dahmane, R.; Hours, A.; Lesage, D.; Tabet, J. C.; Goddard, J. P.;

Toste *et. al*[44] developed their enantioselective cyclopropanation reaction which involved the 1,2-acyloxy migration of a pivaloyl ester (scheme 1. 11).

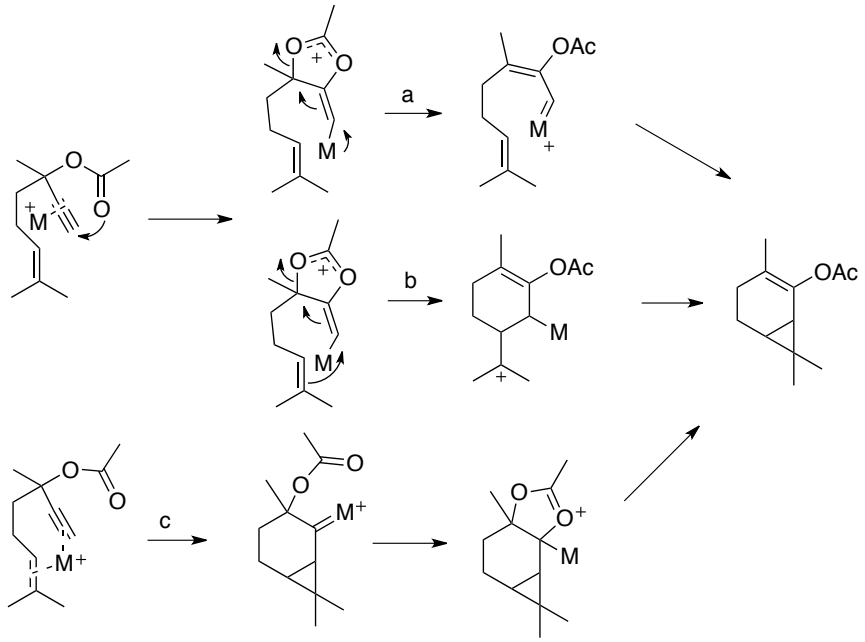


Scheme 1. 11. Gold catalyzed intermolecular cyclopropanation.

This way of using propargylic esters as vinylcarbene precursors (the Ohloff process) has been studied computationally deducing three possible pathways (scheme 1. 12).[43] The first two involve a 1,2-acyloxy migration–cyclopropanation sequence while the third involves a cyclopropanation–1,2-acyloxy migration sequence. Carbene intermediates were proposed in pathways **a** and **c**.

Gandon, V.; Cavallo, L.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Chem. Eur. J.* **2009**, *15*, 3243-3260.

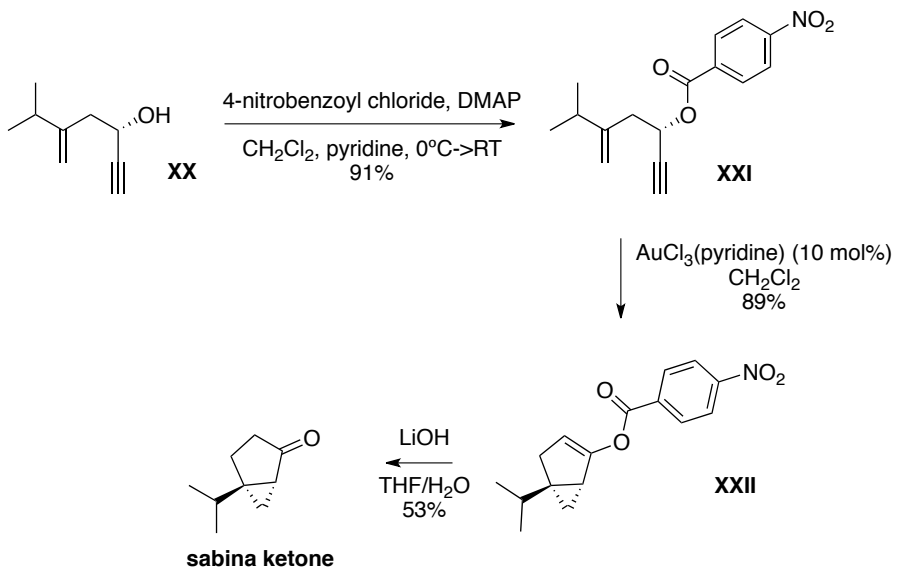
[44] Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.



Scheme 1. 12. Three possible pathways for the Ohloff process.

Gold-catalyzed cycloisomerization of 1,6-enynes, bearing different propargylic esters, was utilized by the group of Fürstner for the synthesis of natural product families such as sesquisabinenes and sesquithujenes.[45] The gold cyclization step involves a 1,2-acyloxy migration, resulting in a cyclopentanone core that is present in all of the final compounds. For the final stereochemical assignment, sabina ketone was synthesized (scheme 1. 13).

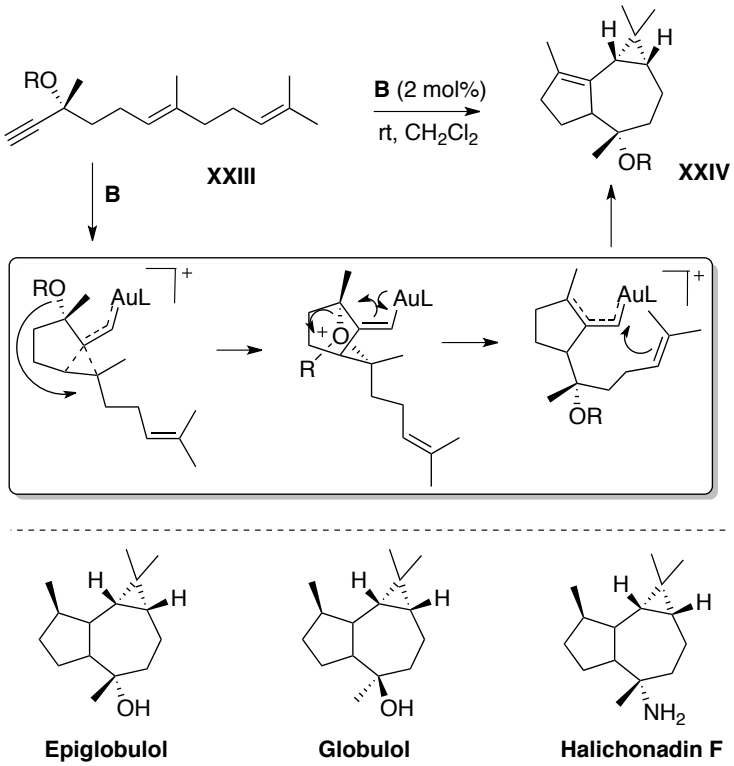
[45] Fürstner, A.; Schlecker, A. *Chem. Eur. J.* **2008**, *14*, 9181-9191.



Scheme 1. 13. Total synthesis of sabina ketone.

In relation to this it was discovered that 1,6-enynes bearing propargylic ethers undergo 1,5-migration of the ether moiety under gold cyclization conditions.[46] This discovery was used for the synthesis of carboskeletons resembling natural products epi-globulol, globulol and halichonadin F. Cycloisomerization of enynes (**XXIII**) gave the tricyclic products **XXIV** in variable yields (scheme 1. 14). The migration occurs through the formation of allyl gold cations followed by an intramolecular cyclopropanation reaction giving the tricyclic product.

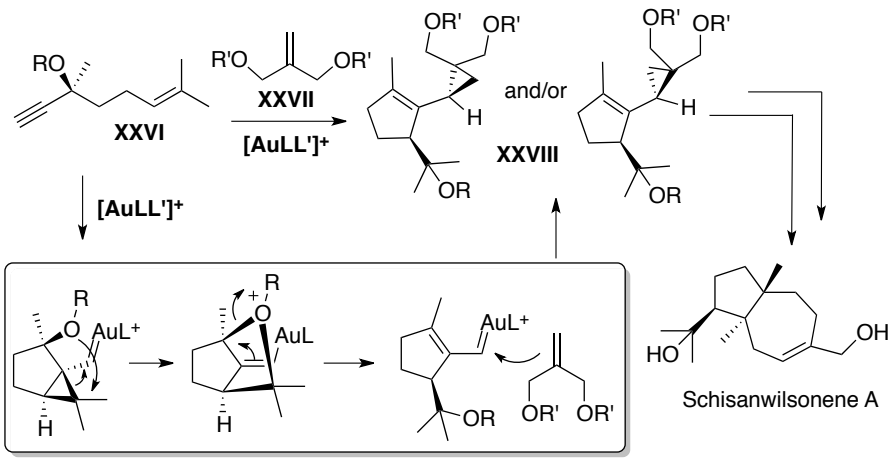
[46] Jiménez-Núñez, E.; Raducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6152-6155.



Scheme 1. 14. 1,5-migration of progargylic ether in the cyclization of 1,6-enyne XXIII

In relation to this discovery it was also found that an intermolecular trapping of the formed allyl gold intermediate could be successfully achieved when adding dienes (**XXVI**) to the reaction mixture. The cationic gold intermediate is trapped by an intermolecular cyclopropanation resulting in divinylcyclopropane products (**XXVII**), which gives a straightforward access to the bicyclic natural product schisanwilsonene A (scheme 1. 15).[47]

[47] Gaydou, M.; Miller, R. E.; Delpont, N.; Ceccon, J. Echavarren, A. M. *Angew. Chem. Int. Ed.* **2013**, 52, 6396-6399.



Scheme 1. 15. Total synthesis of schisanwilsonene A.

Objectives

Epi-globulol and globulol belong to a sesquiterpene family that has been found in a broad spectrum of plant species (figure 1. 6).[48] Aromadendrene can be distilled from *Eucalyptus globulus* and is reperesentative for this group of tricyclic compounds. Hydroxylated derivatives of aromadendrene such as globulol, epiglobulol, ledol and viridiflorol were synthesized and it was found that they possess an antifungal property.

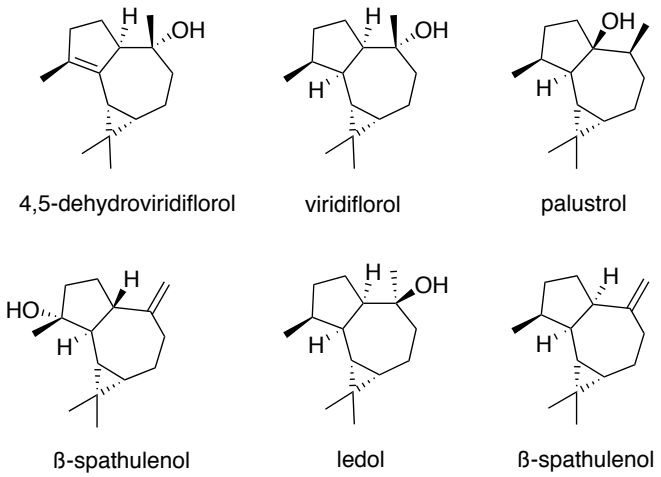
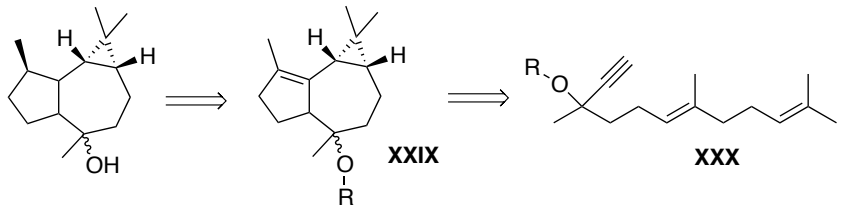


Figure 1. 6. Sesquiterpene family.

With the gold catalyzed cycloisomerization reaction as the key step we made a retrosynthetic plan for the exploration of these kinds of compounds (scheme 1. 16). We envisioned arriving to the final compound through a stereoselective hydrogenation of the unsaturated intermediate (**XXIX**), that would come from the gold catalyzed cycloisomerization step of dienyne (**XXX**), involving the 1,5 migration of the propargylic ether moiety (OR), and subsequent cyclopropanation reaction of the intermediate gold carbene by the second olefin. The dienyne would be synthesized according to

[48] Gijsen, H. J. M.; Wijnberg, J. B. P. A.; Stork, G. A., de Groot, A. *Tetrahedron* **1992**, *12*, 2465-2476.

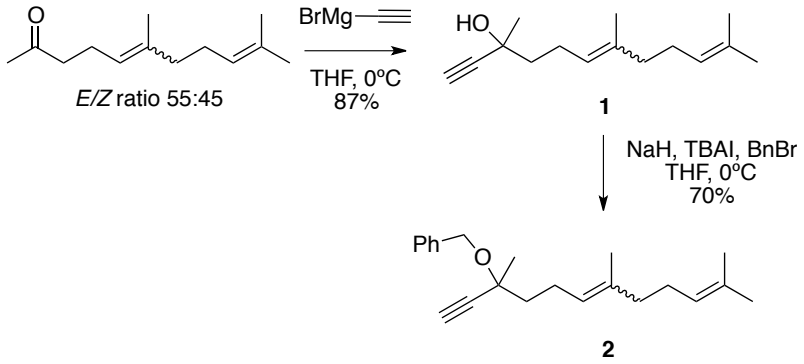
previously known methods starting from commercially available geranyl acetone.[46]



Scheme 1. 16. Retrosynthetic plan for the synthesis of epi-globulol and globulol.

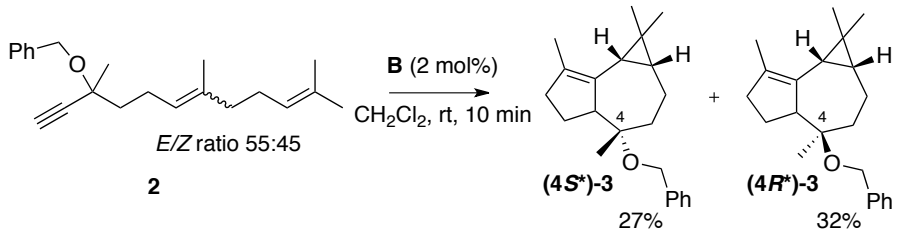
Results

As had been established previously in our group,[46] benzyl protected 1-6-dienyne (**2**) could be prepared in two steps consisting of a Grignard reaction of ethynyl magnesium bromide to commercially available geranyl acetone (*E/Z* mixture 55:45), followed by protection of the formed alcohol with benzyl bromide (Scheme 1. 17).



*Scheme 1. 17. Synthesis of benzyl protected 1,6-dienyne (**2**).*

Using the optimized conditions from the previous results gave full conversion of the starting dienyne **2** into tricyclic compounds **3** as two epimers (scheme 1. 18) catalyzed by cationic gold(I) complex bearing the Johnphos ligand. It was found that the reaction requires a high dilution (0.05 M) and a slow addition of the catalyst in solution. A screening of previously non-tested catalysts was performed (figure 1. 7).



*Scheme 1. 18. Cycloisomerization of dienyne **2** catalyzed by gold complex **B**.*

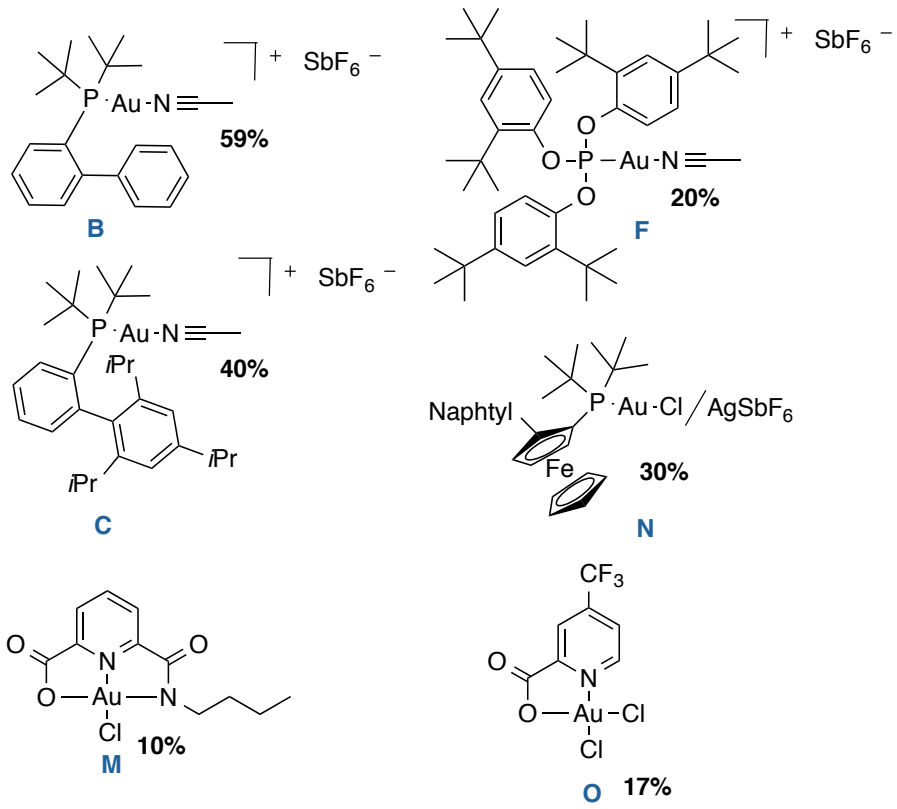


Figure 1. 7. Small screening of different gold catalysts.

Gold complexes bearing phosphine ligands seemed to give the best results. Therefore, two newly synthesized phosphine gold complexes from our group were tested and further used as ligands for our gold complex. Complex **C** with the phosphine ligand bearing isopropyl groups gave a more complex mixture of compounds than complex **B**. Complex **N** with the phosphine ligand bearing a ferrocenyl moiety gave clean product formation albeit with a lower yield. We were also interested to see if the oxidation state of the gold center could change the reaction outcome. We tried two different Au(III) complexes **M** and **O**, but the reaction was slower and low yielding. After this small screening we decided to go on with complex **B** bearing the Johnphos ligand, since none of the new complexes gave any

improvement in the reaction outcome, and complex **B** is commercially available.

The reaction time is very short, leading to full conversion in less than ten minutes. Since the starting material is a 55:45 mixture of isomers two epimers are formed at position 4 of the cyclized product. The two epimers are surprisingly well differentiated on silica gel, the 4*R*-epimer resulting from the *Z*-dienyne has a considerably higher Rf value compared to the 4*S*-epimer resulting from the *E*-dienyne when using cyclohexane/EtOAc (98:2) as eluent (figure 1. 8).

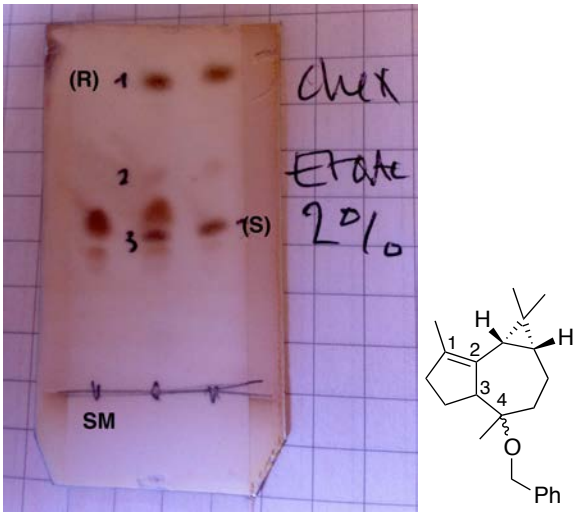


*Figure 1. 8. Thin layer chromatography plate showing the large difference in polarity between spot 1 (**4R*)-3** and spot 3 (**4S*)-3**.*

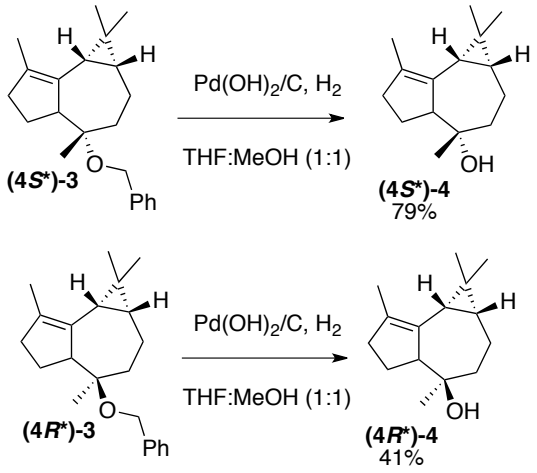
(4*R)-3** can therefore easily be separated from (**4*S**)-3** and as well from other byproducts. (**4*S**)-3** was isolated as a mixture with a minor byproduct and was used in the next step without further purification.

It had been observed previously that lowering the temperature gave no improvement in the reaction outcome.[46] However, we presumed that we could avoid byproduct formation by performing the reaction at lower

temperature. Unfortunately, after performing the reaction at 0ºC, -20ºC and -40ºC we could clearly see that even a slight lowering of the temperature to 0ºC gave decreased selectivity and even new byproducts. This result is most probably due to decomposition of the cyclopropyl gold carbene intermediate. It seems that the intramolecular cyclopropanation with the second alkene requires at least room temperature so that the reaction takes place efficiently.

The deprotection of the benzyl ether required some initial screening to find the right conditions. Deprotection of benzyl-protected ethers is usually performed with Pd/C as catalyst under a H_2 atmosphere in solvents such as methanol or THF.[49] However, the use of Pd/C as catalyst under 1 atm of H_2 in THF: methanol mixture in a 1:1 ratio gave no sign of deprotection on (**4*R***)-3** or (**4*S***)-3**. Increasing the pressure of H_2 in a Parr-vial gave some product formation but even after several days of stirring and addition of more Pd catalyst the conversion did not improve. The reaction was then run in a high-pressure autoclave under 10 bar of H_2 using Pd/C as the catalyst for three days. The TLC analysis of the reaction still showed starting material present, mildly acidic NH_4Cl was therefore added to catalyze the reaction and the H_2 pressure was increased to 20 bar. After 2 days the reaction was stopped even though there was still starting material remaining. Purification of the product by preparative TLC provided the desired free alcohol in 40% yield. However, when changing the catalyst to $Pd(OH)_2/C$ we found that the reaction proceeded smoothly with 100% conversion under one atmosphere of H_2 in a normal round-bottomed flask (scheme 1. 19). The products were easily purified by column chromatography and isolated in 79% yield of the 4*S*-epimer and 41% of the 4*R*-epimer.

[49] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: NewYork, NY, **1999**.



Scheme 1. 19. Deprotection of benzyl ether.

The next step of the synthesis was the selective reduction of the tetrasubstituted double bond in the five membered ring. Selective hydrogenation of olefins with different degrees of substitution is a widely investigated topic, especially within organometallic chemistry.[50] Most transition metals have been tried with an array of structurally different ligand scaffolds. However, hydrogenation of alkenes with tetrasubstituted double bonds remain a challenge.[51] Crabtree's catalyst (**P**) with its iridium center successfully reduces a wide range of olefins, including tetrasubstituted ones.[52] Following Crabtree, Pfaltz and coworkers reported similar iridium complexes bearing chiral phosphine-oxazoline ligands proving very successful both in activity and selectivity.[53] This group has subsequently improved the catalyst by ligand alterations and successfully

[50] Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272-3296.
[51] (a) Dupau, P.; Bruneau, C.; Dixneuf, P. H. *Adv. Synth. Catal.* **2001**, *343*, 331-334. (b) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570-9571. (c) Troutman, M. V.; Appella, D. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4916-4917. (d) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513-531.
[52] Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331-338.
[53] von Matt, P.; Pfaltz A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 12569-12570.

investigated the role of counter anions as well.[54] Alongside iridium, ruthenium[55] has also been used for these types of reductions, as well as rhodium,[56] zirconium[57] and by hydrosilylation catalyzed by Lewis acids.[58]

Due to the slight bend of the fused 7 and 5 membered rings, the side from which the hydride needs to enter is more sterically hindered (as can be seen in figure 1. 9. in the crystal structure of (**4*S**)-3**). This type of reaction has also been explored in our group before and especially in the synthesis of englerin A[59] where one of the steps required a reduction of a tetrasubstituted olefin.

[54] Roseblade, S. J.; Pfaltz A. *Acc. Chem. Res.* **2007**, *40*, 1402-1411. Lightfoot, A.; Schnider P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2897-2899. Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hörmann, E.; McIntyre, S.; Menges, F.; Schönleber, M.; Schmidt, S. P.; Wüstenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2002**, *345*, 33-44. Schrems, M. G.; Neumann, E.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8274-8276.

[55] Dobbs, D. A.; Vanhessche, K. P. M.; Brazi, E.; Rautenstrauch, V.; Lenoir, J. Y.; Genet, J. P.; Wiles, J.; Bergens, S. H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1992-1995.

[56] Budzelaar, P. H. M.; Moonen, N. N. P.; de Gelder, R.; Smits, J. M. M.; Gal, A. W. *Eur. J. Inorg. Chem*. **2000**, *4*, 753-769.

[57] Troutman, M. V.; Appella, D. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4916-4917.

[58] Oertle, K.; Wetter, H. *Tet. Lett.* **1985**, *26*, 5511-5514.

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

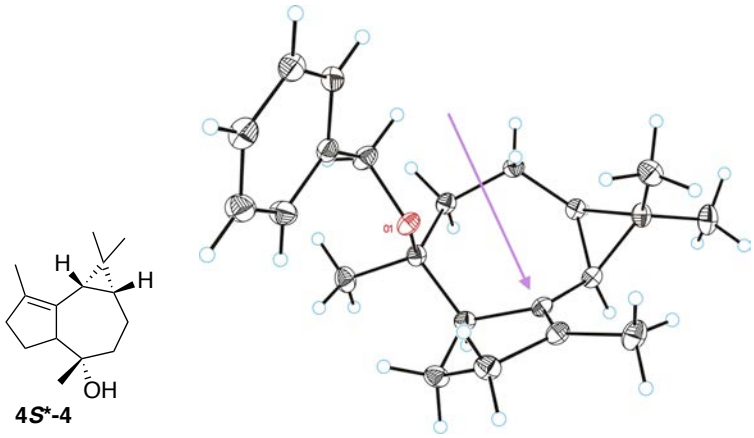
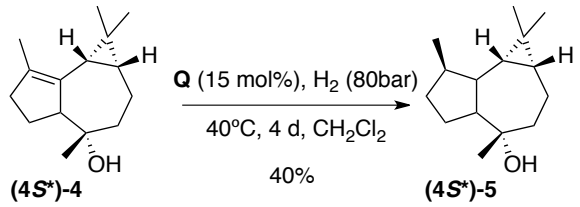


*Figure 1. 9. Crystal structure of **(4S*)-3** indicating the phase from where the hydride needs to enter when reducing the double bond in **(4S*)-4**.*

A screening of well-known hydrogenation catalysts was performed. Both iridium (entries 1-5, 7, 9, table 1. 1) and rhodium (entries 6, 8) were tested in CH_2Cl_2 or dichloroethane as solvent, with varying pressures of H_2 gas. Only the iridium catalyst (**Q**) derived from Crabtree's catalyst (**P**) bearing BAr_F ([tetrakis(3,5-bis(trifluoromethyl)phenyl)borate]) as the counteranion gave any conversion to the product. After 4 days of stirring under an 80 bar pressure of H_2 at 40ºC, the product, epi-globulol (**(4*S**)-5**), could be isolated in 40% yield (scheme 1. 20). This natural compound can be purchased from Sigma-Aldrich (CAS: 88728-58-9), naturally leading to a quick confirmation of the reaction outcome. The reduction proceeds most likely through the coordination of the OH functional group to the iridium metal center, directing the hydride from the more hindered phase. The low conversion and yield is probably due to the sterical hindrance exerted by the slight bend of the molecule at the ring junction as well as the high substitution of the double bond. Increasing the temperature only led to decomposition of the starting material. Methanolic solutions of platinum oxide (entry 10), supported rhodium (entry 11) and palladium hydroxide (entry 12) were also tested for their ability to reduce the olefin. However, none of the tested conditions gave any product.

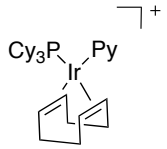


Scheme 1. 20. Hydrogenation of tetrasubstituted double bond.

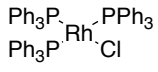
*Table 1. 1. Hydrogenation of tetrasubstituted double bond in **(4S*)-4**.*[a]

Entry	[M]	T	Solvent	Yield
1	**Q**	rt	CH_2Cl_2	n.r
2	**Q**	rt	CH_2Cl_2	Product visible on TLC
3	**Q**	40ºC	CH_2Cl_2	40%
4	**Q**	80ºC	$C_2H_4Cl_2$	n. r.
5	**P**	40ºC	CH_2Cl_2	n. r.
6	**R**	50ºC	$C_2H_4Cl_2$	n. r.
7	**S**	50ºC	$C_2H_4Cl_2$	n. r.
8	**T**	50ºC	$C_2H_4Cl_2$	n. r.
9	**Q**	50ºC	$C_2H_4Cl_2$	n. r.
10	PtO_2	50ºC	MeOH/THF	n. r.
11	Rh/C	50ºC	MeOH/THF	n. r.
12	$Pd(OH)_2/C$	50ºC	MeOH/THF	n. r.

[a]**(4*S**)-4** (1 eq) was put in an autoclave under argon together with the chosen catalyst (0.1-0.5 eq) and put under an 80 bar pressure for four days at indicated temperature and in indicated solvent (0.1M). Reactions were monitored by TLC. When completed the autoclave was carefully depressurized and the catalyst was filtered off.



P PF_6^- salt
Q BAr_F^- salt



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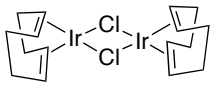

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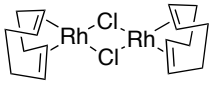
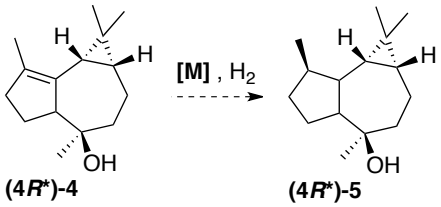


T

We performed the same screening of reduction conditions with the 4*R*-epimer of **4** in the hopes of finding a way of reducing the olefin in a similar manner to that of the 4*S*-epimer. The biggest obstacle we faced in this situation was the missing coordinating group to direct the incoming hydride, as happens for the **(4*S**)-4**. The OH is sitting in the axial position in the 4R-epimer and therefore points away and upward on the convex phase, away from the olefin. Unfortunately, trying transition metals to which the OH has a pronounced affinity, such as iridium or rhodium, did not lead to any reduction of the double bond. Our conclusion from this, with the aid of the structural information provided by the crystal structure that was obtained, is due to that the OH-[M] interaction lies too far away from the olefin resulting in no coordinative assistance for the reduction. Therefore, we decided to screen a different set of catalysts, which normally do not establish stable complexes with OH, in the hopes of finding some reductive conditions that could lead us to the selective reduction towards globulol (scheme 1. 21, table 1. 2). Unfortunately none of the conditions we tried led to any product formation.



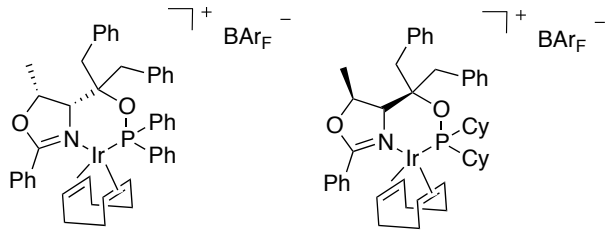
(4*R)-4** **(4*R**)-5**

Scheme 1. 21. Hydrogenation of tetrasubstituted double bond.

*Table 1. 2. Hydrogenation of double bond on **(4R*)-4**.*[a]

Entry	[M]	Temperature	Solvent	Yield
1	**T**	40ºC	CH_2Cl_2	decomposition
2	**S**	40ºC	CH_2Cl_2	decomposition
3	**R**	40ºC	CH_2Cl_2	decomposition
4	$Pd(OH)_2/C$	40ºC	MeOH/THF	n. r.
5	**Q**	40ºC	CH_2Cl_2	n. r.
6[b]	**U**	rt	CH_2Cl_2	cleavage of hydroxyl group
7[b]	**V**	rt	CH_2Cl_2	n. r.

[a]**(4*R**)-4** (1 eq) was put in an autoclave under argon together with the chosen catalyst (0.1-0.5 eq) and put under an 80 bar pressure for four days at indicated temperature and with indicated solvent (0.1M). Reactions were monitored by TLC. When completed the autoclave was carefully depressurized and the catalyst was filtered off. [b] Reactions performed by Dr. Paul McGonigal



U **V**

Another interesting target molecule within the same terpenoid family is aromadendranediol, which has the same 3-5-7 tricyclic core as epi-globulol and globulol. It was isolated the first time from the *Sinularia maxima* coral together with nine other terpenoids by the group of Anjaneyulu in 1995,[60] as well as from the leaves of the Amazonian tree *Xylopia brasiliensis.*[61] It was later tested by Gijsen et. al for its antibacterial activities through a minimal inhibitory concentration test (MIC) and a thin-layer bioautography test.[62] However, the activities were found to be low to moderate in both tests. Despite this fact the plant is known to have been used in both Chinese[63] and Brazilian[61] traditional medicine as sedatives, analgesics and to treat pneumonia. A semisynthesis was reported by Djerrasi and co-workers starting from (+)-spathulenol. [64] The total synthesis of (-)-aromadendranediol was performed in the group of McMillan in 2009 through an organocatalyzed route.[65]

We envisioned the synthesis of (±)-aromadendranediol starting from intermediate **(4*R**)-4** with an initial epoxidation of the double bond in the cyclopentene ring by treatment with mCPBA. The epoxide would then be opened by reduction giving the expected-diol product (Scheme 1. 22).[66] The reactions were carried out by Dr. Paul McGonigal and gave excellent yields in both steps giving a direct access to (±)-aromadendranediol. Its structure was confirmed after comparison to the NMR data obtained in the previous syntheses.[64,65]

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[60] Anjaneyulu, A. S. R.; Sagar, K. S.; Venugopal, M. J. R. V. *Tetrahedron* **1995**, *51*, 10997-11010.

[61] Moriera, I. C.; Lago, J. H. G. ; Young, M. C. M.; Roque, N. F. *J. Braz. Chem. Soc.* **2003**, *14*, 828-831.

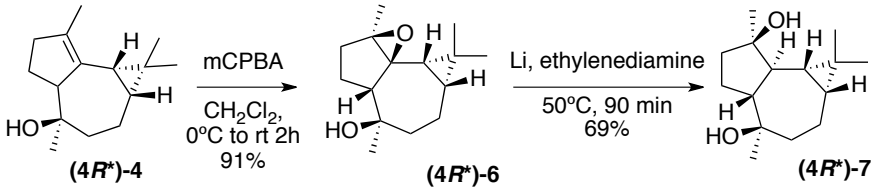
[62] Gijsen, H. J. M.; Wijnberg, J. B. P. A.; Stork, G. A.; de Groot, A.; de Waard, M. A.; van Nistelrooy, J. G. M. *Tetrahedron* **1992**, *48*, 2465-2476.

[63] Wu, T.; Chan, Y.; Leu, Y. *Chem. Pharm. Bull.* **2000**, *3*, 357 – 361.

[64] Beechan, C. M.; Djerassi, C.; Eggert, H. *Tetrahedron* **1978**, *34*, 2503 – 2508.

[65] Simmons, B.; Walji, A. M.; McMillan, D. W. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4349-4353.

[66] Brown, H. C.; Ikegami, S.; Kawakami, J. H. *J. Org. Chem.* **1970**, *35*, 3243-3245.



*Scheme 1. 22. Synthesis of ±Aromadendranediol, **(4R*)-7**.*

We were also interested in using our developed strategy for dienynes bearing a propargylic amine rather than an alcohol for the synthesis of natural compounds such as the sesquiterpenes halichonadins E and F.

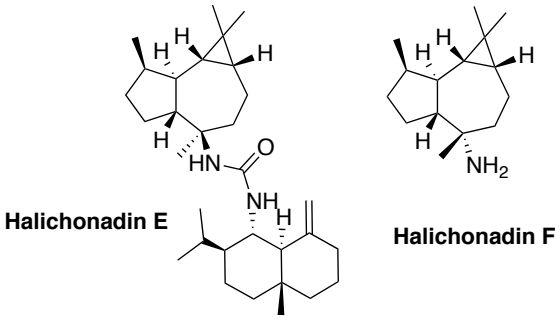
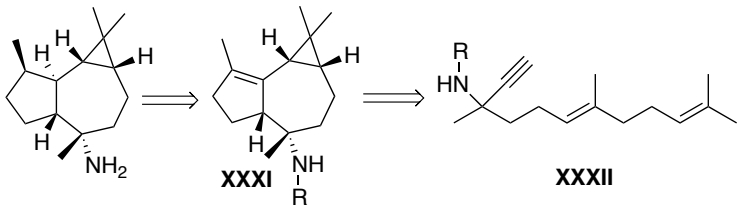


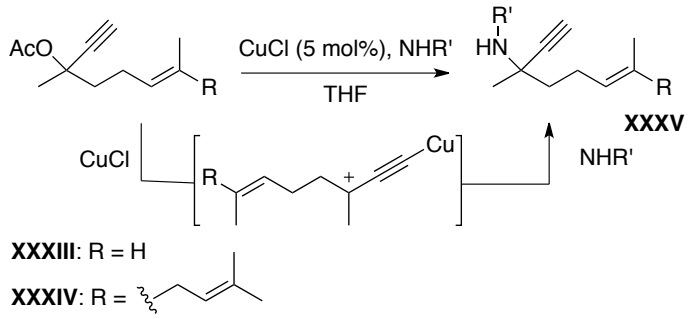
Figure 1. 10. Halichonadin E and F.

We envisioned the synthesis of these natural compounds to be accessible through the same strategy as the one we had developed for epi-globulol and globulol (scheme 1. 23). Different 1,6-enynes (**XXXII**) would be constructed bearing the propargylic amine moiety which would cycloisomerize in the same manner as had been seen before with dienynes bearing a propargylic ether. The amino group would undergo a 1,5-migration and result in the tricyclic core (**XXXI**) that is present in all these molecules.



Scheme 1. 23. Retrosynthetic analysis for halichonadin F.

We compiled a small family of enynes bearing a propargyl amine moiety (figure 1. 11). We found that the basicity of the starting aniline or amine, needed to be quite strong for the coupling to the enyne to occur. However, when employing the acetyl protected enyne (**XXXIII** or **XXXIV**) in the presence of CuCl its allene intermediate was formed, which undergoes a nucleophilic attack from amines resulting in a propargylic amine **XXXV**[67] (scheme 1. 24).



Scheme 1. 24. Copper-catalyzed amination of 1,6-enynes.

[67] Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S.-I. *J. Org. Chem.* **1994**, *59*, 2282-2284.

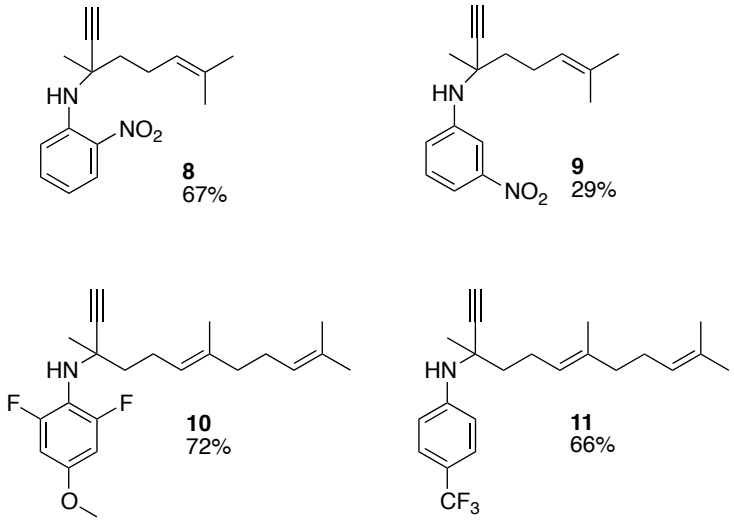
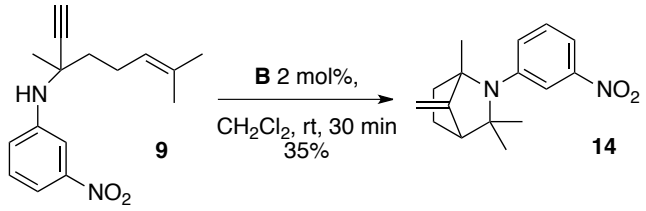


Figure 1. 11. Small library of 1,6-enynes bearing progargylic amines.

Unfortunately when attempting to cyclize these enynes under the previously optimized conditions, only enyne **9** gave the cyclization product **14** in low yield (scheme 1. 25). We hypothesized that the basic amine slows down the gold-catalyzed cyclization by coordination to LAu^{+}.



*Scheme 1. 25. Gold catalyzed cycloisomerization reaction of 1,6-enyne **9**.*

Conclusions

We were able to successfully synthesize racemic epiglobulol in a 5-step synthetic route with an overall yield of 16%, starting from commercially available geranyl acetone. Further derivatization was made from the (4*R*)-epimer of one of the intermediates to gain access to racemic aromadendranediol in a 6 step synthetic route with an overall yield of 11%. The syntheses of the enantiomerically pure versions of these two natural products are currently being developed in our research group starting from commercially available *trans*,*trans*-farnesol.

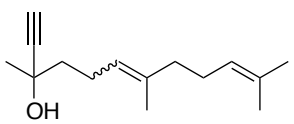
A retrosynthetic pathway was envisioned for the synthesis of natural compounds halichonadin E and F and a small library of progargyl-amine-functionalized enynes and dienynes were synthesized. However, the cyclizations of these amine-enynes were in most cases unsuccessful.

Experimental part

General methods

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 GF234). Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm). NMR spectra were recorded at 23ºC on a Bruker Avance 400 Ultrashield and on a Bruker Avance 500 Ultrashield apparatus. For some compounds DEPTQ NMR spectra (Polarization Enhancement Nurtured During Attached Nucleus Testing) are provided instead of standard ^{13}C NMR spectra. Mass spectra were recorded on a Waters LCT Premier spectrometer (ESI and APCI) or on a Autoflex Bruker Daltonics (MALDI and LDI). Semiprerarative HPLC was performed on a Waters system using a Spherisorb® S5W column (20x250 mm). Melting points were determined using a Büchi melting point apparatus. Iridium catalyst (**B**) was synthesized according to literature procedure.[68]

Benzyl protected dienyne (**1**) was synthesized according to a somewhat modified literature procedure.[69]



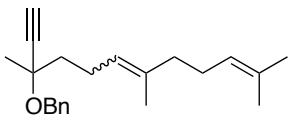
(**1**): Geranyl acetone (3.4 mL, 15 mmol, 1 eq) (*E/Z* ratio 55:45) was dissolved in 150 mL THF and cooled down to 0ºC. Ethynylmagnesium bromide (45 mL, 0.5 M solution in THF, 22.5 mmol, 1.5 eq) was then added dropwise by syringe pump over 30 min. The reaction was monitored by TLC and when the starting material had been consumed the reaction was quenched with a saturated solution of NH_4Cl. The two phases were separated and the organic phase was washed with water followed by brine. The organic phase was then dried over Na_2SO_4 and concentrated. The product was purified by bulb-to-bulb distillation in a *Kugelrohr* apparatus. At a vacuum of 4 mbar the product is distilled at 160ºC as a colorless oil (2.9 g, 87%). ^1H NMR (500 MHz, $CDCl_3$) δ 5.20-5.15 (m, 1H), 5.13-

[68] Wüstenberg, B; Pfaltz, A. *Adv. Synth. Catal.* **2008**, *350*, 174-178.

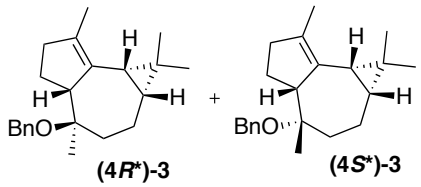
[69] (a) Jiménez-Núñez, E.; Raducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem. Int. Ed*. **2009**, *48*, 6152-6155. (b) Fürstner, A.; Hannen, P. *Chem. Eur. J.* **2006**, *12*, 3006–3019.

5.07 (m, 1H), 2.45 (d, E+Z isomers, 1H), 2.34-1.98 (m, 7H), 1.73-1.56 (m, 12H), 1.50 (d, E+Z isomers, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.4, 131.8, 131.7, 124.5, 124.4, 124.3, 123.7, 71.6, 68.5, 68.4, 43.6, 43.3, 39.9, 32.1, 29.9, 26.8, 26.7, 25.8, 23.6, 23.5, 23.5, 17.8, 16.2. HRMS-APCI+: *m/z* calcd for $C_{15}H_{23}$: 203.1794; found 203.1799.

NMR data are in accordance with previously reported analysis[69b] with the addition of the signals from both isomers.



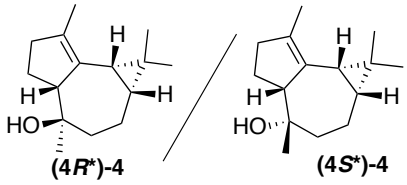
(**2**): Dienyne (**1**) (1g, 4.6 mmol, 1 eq) was dissolved in THF (2 mL) and added slowly over a THF solution (3 mL) of NaH (370 mg, 9.2 mmol, 2 eq) at 0ºC under argon. Gas evolution could be seen. The solution was kept at 0ºC until no more gas bubbles could be seen (1-3h). A solution of TBAI (98 mg, 0.26 mmol, 0.05 eq) and benzyl bromide (0.66 mL, 5.5 mmol, 1.2 eq) in THF (6 mL) was then added. The solution was allowed to warm to room temperature and left stirring until (**1**) had been completely consumed (TLC). The reaction was carefully quenched with the addition of water (CAREFUL! Gas evolution) at 0ºC. The two phases were then separated and the organic phase was washed with brine. The organic phase was then dried over Na_2SO_4 and concentrated. Purification was made by column chromatography on a ISCO Combiflash *Companion* system, with a gradient from 100% cyclohexane/0% EtOAc to 100% EtOAc over a 120g RediSep R_f Silica cartridge, giving the product as a colourless oil (1.0 g, 3.2 mmol, 70%). NMR data were in accordance with previously reported analysis.[69a] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.23 (m, 4H), 7.20-7.16 (m, 1 H), 5.10-5.01 (m, 2H), 4.62-4.59 (d, J = 11.0 Hz, 1H), 4.55-4.52 (d, J = 11.0 Hz, 1H), 2.43 (s, *E* isomer, 1H), 2.42 (s, *Z* isomer, 1H), 2.22-2.09 (m, 2H), 1.99-1.97 (m, 3H), 1.93-1.88 (m, 1H) 1.79-1.64 (m, 2H), 1.61 (*b*s, 4H), 1.53 (s, 3H), 1.46-1.44 (m, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 139.8 (C), 135.5 (C), 131.2 (C), 128.5 (CH), 128.3 (CH), 127.8 (CH), 127.4 (CH), 125.3 (CH), 124.9 (CH), 124.4 (CH), 85.5 (C), 73.8 (CH), 73.6 (C), 66.5 (CH_2), 42.6 (CH_2), 40.2 (CH_2), 32.2 (CH_2), 27.2 (CH_2), 26.5 (CH_3), 17.8 (CH_3), 16.1 (CH_3). HRMS-APCI+: *m/z* calcd for $C_{22}H_{31}O$: 311.2369; found 311.2371.



(4*R)-3/(4*S**)3:** (Acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate (**B**) (24 mg, 0.032 mmol, 0.2 mol%) was dissolved in dry CH_2Cl_2 (0.05 M) and added dropwise over a stirred solution of the dienyne (**2**) (510 mg, 1.6 mmol) in CH_2Cl_2 (0.05 M) with activated molecular sieves (4 Å). The reaction mixture was stirred until all starting dienyne had been consumed (TLC) and was then quenched by a 10% solution of Et_3N in hexane, filtered through a pad of silica and concentrated. The two epimers were separated by column chromatography (Eluent cy-Hex/EtOAc 95:5) in 59% yield ((4*R**)-3, 139 mg, 0.45 mmol, 27%), ((4*S**)-3, 164 mg, 0.52 mmol, 32%).

(4*R)-3:** ^{1}H NMR (500 MHz, C_6D_6) δ 7.34 (d, *J* = 7.3, 2H), 7.19 (t, *J* = 7.5, 2H), 7.06 (t, *J* = 7.3, 1H), 4.23 (d, *J* = 11.4, 1H), 4.15 (d, *J* = 11.4, 1H), 2.67 (m, 1H), 2.57 (*b*d, *J* = 8.7, 1H), 2.32-2.25 (m, 1H), 2.12-2.06 (m, 1H), 1.99-1.82 (m, 2H), 1.70 (s, 3H), 1.68-1.61 (m, 2H), 1.43-1.38 (m, 2H), 1.14 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 0.75-0.68 (m, 1H). ^{13}C NMR (126 MHz, DEPTQ, C_6D_6) δ 140.8 (C), 139.7 (C), 133.0 (C), 128.4 (CH), 127.0 (CH), 126.8 (CH), 79.2 (C), 63.1 (CH_2), 62.1 (CH_3), 37.5 (CH_2), 36.5 (CH_2), 28.9 (CH_3), 27.2 (CH), 27.1 (CH), 25.9 (CH_2), 25.7 (CH), 21.4 (C), 19.3 (CH_2), 17.8 (CH_3), 16.4 (CH_3). HRMS-ESI+: *m/z* calcd for $C_{22}H_{30}NaO$: 333.2189; found 333.2184.

The NMR data of **(4*S**)-3** corresponded to previously reported data.[69a] Crystals suitable for X-ray diffraction were grown from slow evaporation of a saturated CH_2Cl_2:pentane solution.

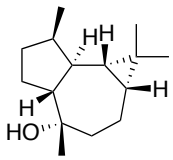


(4*R)-4/(4*S**)-4**: The two epimers of the protected cyclized dienyne (**(4*S**)-3**, 797 mg, 2.6 mmol) (**(4*R**)-3**, 840 mg, 2.7 mmol) were put in different 25 mL round bottomed flasks. The vessels were both charged with $Pd(OH)_2/C$ (210 mg, 1.5 mmol) each and were dissolved in 10 mL of

methanol and THF in a 1:1 mixture. The flasks were sealed with septa and evacuated of air and refilled with H_2 gas from a balloon three times. The flasks were then left stirring under H_2 gas until all starting material had been deprotected (TLC). The products were then filtered over a pad of celite to remove the palladium catalyst. The solutions were concentrated and purified by flash column chromatography.

(4*R)-4**: eluent cy-Hex/EtOAc 10:1, beige solid in 41% yield (240 mg, 1.1 mmol). Crystals suitable for X-ray diffraction were grown from slow evaporation of a saturated MeCN solution. M.p. = 85-89°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.64-2.55 (m, 1H), 2.42-2.29 (m, 1H), 2.11-1.76 (m, 5H), 1.68-1.61 (m, 5H), 1.10 (s, 3H), 1.00 (s, 3H), 0.95 (s, 1H), 0.91-0.78 (m, 1H), 0.71 (td, *J* = 9.8, 7.3 Hz, 1H). ^{13}C NMR (126 MHz, DEPTQ, $CDCl_3$) δ 139.5 (C), 132.5 (C), 77.1 (C), 62.5 (CH), 44.1 (CH2), 37.3 (CH2), 37.1 (CH3), 28.9 (CH3), 28.7 (CH), 26.4 (CH), 25.7 (CH2), 25.4 (CH3), 20.6 (CH3), 20.5 (CH2), 20.0 (C), 17.9 (CH3), 16.1 (CH3). HRMS-APCI+: *m/z* calcd for $C_{15}H_{23}$: 203.1794; found 203.1796.

(4*S)-4**: eluent cy-Hex/EtOAc 5:1, transparent oil in 79% yield (453 mg, 2.1 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66 (bd, *J* = 9.8, Hz, 1H), 2.46 (m, 1H), 2.17-1.85 (m, 3H), 1.76 (dtd, *J* = 14.9, 6.6, 2.0 Hz, 1H), 1.70 (bs, 3H), 1.69-1.59 (m, 2H), 1.22 (s, 3H), 1.14 (s, 3H), 1.05 (s, 3H), 1.02-0.98 (m, 1H), 0.80-0.68 (m, 1H).^{13}C NMR (126 MHz, DEPTQ, $CDCl_3$) δ 141.7 (C), 132.1 (C), 74.7 (C), 60.4 (CH), 41.6 (CH_2), 36.9 (CH_2), 29.8 (CH_3), 28.7 (CH_3), 26.7 (CH), 26.1 (CH), 24.8 (CH_2), 20.9 (C), 19.3 (CH_2), 18.0 (CH_3), 16.1 (CH_3). HRMS-APCI+: *m/z* calcd for $C_{15}H_{23}$: 203.1794; found 203.1792.



(4*S)-5**: (1,5-Cyclooctadiene)(pyridine)(tricyclohexylphosphine)-iridium(I) tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**P**) (106 mg, 0.03 mmol, 0.15 eq) and tricyclic **(4*S**)-4** (100 mg, 0.45 mmol, 1 eq) were dissolved in dry CH_2Cl_2 (0.1M) in an autoclave reactor in the glovebox. The reactor was carefully sealed and removed from the glove box. It was then charged with hydrogen gas (80 bar) and heated to 40ºC over 4 days. The reactor was then carefully depressurized and the solution was filtered

through a pad of silica. The product was purified through column chromatography (eluent cy-Hex/EtOAc 10:1) to give the pure (±)-epiglobulol (**(4*S**)-5**) in 40% yield as a fragrant transparent oil (40 mg, 0.18 mmol). The NMR data matched the NMR data of the commercially available naturally harvested product (Sigma-Aldrich). ^{1}H NMR (500 MHz, C_6D_6) δ 2.08-1.98 (m, 1H), 1.92 (dt, *J* = 11.2, 9.4 Hz, 1H), 1.81-1.71 (m, 1H), 1.67-1.30 (m, 8H), 1.21-1.11 (m, 1H), 1.09 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 0.97 (d, *J* = 7.2 Hz, 3H), 0.66 (s, 1H), 0.50 (ddd, *J* = 11.1, 9.4, 6.0 Hz, 1H), 0.41 (dd, *J* = 11.2, 9.4 Hz, 1H). ^{13}C NMR (126 MHz, DEPTQ, C_6D_6) δ 128.3 (C), 71.6 (CH), 56.0 (CH), 43.4 (CH_2), 37.8 (CH), 36.2 (CH), 35.1 (CH_2), 31.4 (CH_3), 29.2 (CH), 29.0 (CH_3), 27.6 (CH), 26.8 (CH_2), 19.5 (CH_2), 16.9 (CH_3), 16.1 (CH_3). HRMS-APCI: *m/z* calcd for C15H25: 205.1951; found 205.1950 [M-OH]+.

General procedure for synthesis of 1,6-enynes bearing propargylic amine moiety

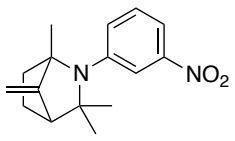
The enyne (200.0 mg, 1.0 mmol) was weighed in a microwave-vial. The amine/aniline (3 equiv) was added together with CuCl (5.0 mg, 0.05 mmol, 5 mol%). The vial was sealed and 3 vacuum-argon cycles were done. 2 mL of dry THF was then added and the reaction was put under microwave conditions at 50ºC until all starting material was consumed (TLC) (normally 1-5h). The reaction was then quenched with the addition of 3.3 equiv. of Et_3N. Water was added to the solution and the two phases were separated. The organic phase was washed once with brine and dried under $MgSO_4$. The solution was concentrated onto Florisil and purified by column chromatography.

***N*-(3,7-dimethyloct-6-en-1-yn-3-yl)-2-nitroaniline (8)**: Flash chromatography using 4% EtOAc in hexane as eluent giving the product in 67% yield (183.4 mg, 0.67 mmol): ^{1}H NMR (500 MHz, C_6D_6) δ 8.37 (bs, 1H), 8.10 (d, J = 8.9 Hz, 1H), 7.51 (d, J = 8.9 Hz, 1 H), 6.92 (t, J = 7.9 Hz, 1H), 6.22 (t, J = 7.9, 1H), 5.05 (m, 1H), 2.31-2.17 (m, 2H), 2.00 (s, 1H), 1.80-1.65 (m, 2H), 1.64 (s, 4H), 1.60 (s, 1H) 1.54 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 135.3, 133.0, 133.0, 127.1, 122.7, 116.6, 116.0, 85.2, 73.3, 51.2, 42.6, 27.8, 25.8, 23.2, 17.7. HRMS-ESI+: *m/z* calcd for $C_{16}H_{20}N_2O_2Na$: 295.1422; found 295.1425.

***N*-(3,7-dimethyloct-6-en-1-yn-3-yl)-3-nitroaniline (9)**: Flash chromatography using 4% EtOAc in hexane as eluent giving the product in 29% yield (77.1 mg, 0.28 mmol): ^{1}H NMR (500 MHz, C_6D_6) δ 7.71-7.70 (m, 1H), 7.47 (d, J = 7.9 Hz, 1 H), 6.83-6.75 (m, 2H), 5.07 (m, 1H), 3.46 (bs, 1H), 2.22-2.03 (m, 2H), 2.00 (s, 1H), 1.64 (s, 3H), 1.64-1.54 (m, 2H), 1.51 (s, 3H) 1.24 (s, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 149.6, 146.7, 132.6, 129.4, 128.4, 123.7, 120.7, 112.7, 110.2, 73.1, 51.6, 41.9, 27.5, 25.7, 23.5, 17.6. HRMS-ESI+: *m/z* calcd for $C_{16}H_{20}N_2O_2Na$: 295.1422; found 295.1423.

(*E*)-2,6-difluoro-4-methoxy-*N*-(3,7,11-trimethyldodeca-6,10-dien-1-yn-3-yl)aniline (10): Flash chromatography using 15% EtOAc in hexane as eluent giving the product in 72% yield (261.2 mg, 0.72 mmol): ^{1}H NMR (500 MHz, C_6D_6) δ 6.36 (d, J = 9.3 Hz, 2H), 5.31-5.21 (m, 2H), 3.14 (bs, 1H), 3.03 (s, 3H), 2.53-2.23 (m, 2H), 2.17 (s, 3H), 2.10-2.07 (m, 1H), 2.02 (s, 1H), 1.89-1.78 (m, 2H), 1.72 (s, 1H), 1.68 (s, 6H), 1.57 (s, 3H), 1.49 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 158.5, 156.7, 136.3, 127.7, 124.5, 120.5, 98.1, 71.5, 55.8, 42.8, 35.3, 32.9, 28.8, 27.2, 23.9, 19.9, 19.7, 17.7, 16.1. HRMS-ESI+: *m/z* calcd for $C_{22}H_{30}F_2ON$: 362.2290; found 362.2286.

(*E*)-4-(trifluoromethyl)-*N*-(3,7,11-trimethyldodeca-6,10-dien-1-yn-3-yl)aniline (11): Flash chromatography using 10% EtOAc in hexane as eluent giving the product in 66% yield (231.5 mg, 0.66 mmol): ^{1}H NMR (500 MHz, C_6D_6, selected signals together with minor impurity) δ 7.31 (d, J = 9.2 Hz, 2H), 6.82 (d, J = 9.21, 2H), 5.06-4.97 (m, 2H), 4.00 (bs, 1H), 2.35 (s, 1H), 2.20-1.69 (m, 12H), 1.59 (s, 3H), 1.50 (m, 9H). ^{19}F NMR (470 MHz, C_6D_6) δ -60.90 (s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 136.5, 131.6, 126.3, 124.3, 123.2, 114.7, 85.9, 72.5, 51.5, 42.1, 39.8, 27.8, 26.8, 25.8, 23.2, 17.8, 16.1. HRMS-ESI+: *m/z* calcd for $C_{22}H_{27}F_3N$: 362.2101; found 362.2098.



1,3,3-trimethyl-7-methylene-2-(3-nitrophenyl)-2-azabicyclo[2.2.1]heptane (**14**): Progargylic amine enyne (**9**) (72.1 mg, 0.28 mmol) was dissolved in 2.5 mL of dry CH_2Cl_2 and transferred in to a vial containing molecular sieves under argon. (Acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I)

hexafluoroantimonate (**B**) (22.0 mg, 0.028 mmol, 10 mol%) was dissolved in 0.5 mL of dry CH_2Cl_2 and added dropwise to the dissolved enyne. The reaction was allowed to stir until all enyne had been consumed (TLC) and was then quenched by the addition of a 10% Et_3N solution in hexane. The solution was then filtered through a small pad of silica and concentrated. The crude reaction mixture was concentrated on to Florisil and purified by column chromatography using 1.5% EtOAc in hexane as eluent giving the product (**14**) as a yellow colored oil in 35% yield (27.0 mg, 0.09 mmol). : ^{1}H NMR (500 MHz, C_6D_6) δ 7.79 (m, 1H), 7.52-7.49 (m, 1 H), 6.79-6.77 (m, 2H), 4.64 (s, 1H), 4.57 (s, 1H), 2.06-199 (m, 1H), 1.84 (d, J = 4.5 Hz, 1H), 1.56-1.50 (m, 1H), 1.35-1.29 (m, 1H), 1.28 (s, 3H), 1.21 (s, 3H), 1.16-1.07 (m, 1H) 0.90 (s, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 157.0, 149.2, 146.5, 128.7, 124.6, 113.2, 112.2, 96.5, 65.1, 64.4, 53.2, 30.5, 29.7, 23.5, 22.3, 20.6, 15.7. HRMS-ESI+: *m/z* calcd for $C_{16}H_{20}N_2O_2Na$: 295.1417; found 295.1422.

Crystal structures

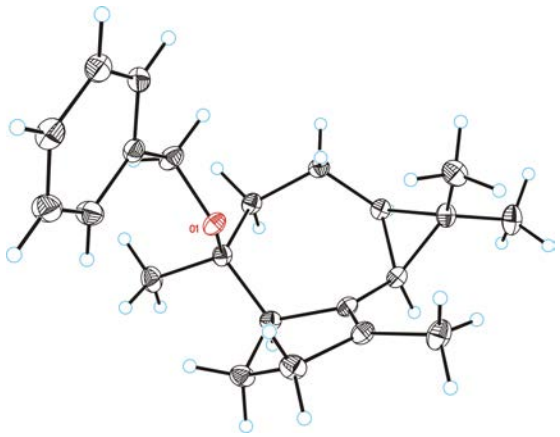


Table 1. Crystal data and structure refinement for **(4*S**)-3**.

Identification code	MLc53_0m
Empirical formula	C22 H30 O
Formula weight	310.46
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 8.9044(4) Å
⟨= 82.296(2) °.	
	b = 9.3413(4) Å
® = 82.864(2) °.	
	c = 10.7520(5) Å
© = 88.700(2) °.	
Volume	879.38(7) Å^3
Z	2
Density (calculated)	1.172 Mg/m^3

Absorption coefficient	0.069 mm^{-1}
F(000)	340
Crystal size	0.40 x 0.20 x 0.15 mm^3
Theta range for data collection	1.93 to 41.23 °.
Index ranges	-16 <=h<=16 ,-17 <=k<=16
,-19 <=l<=19	
Reflections collected	39501
Independent reflections	10469 [R(int) = 0.0435]
Completeness to theta =41.23 °	0.891 %
Absorption correction	Empirical
Max. and min. transmission	0.9897 and 0.9729
Refinement method	Full-matrix least-squares on
F^2	
Data / restraints / parameters	10469 / 0 / 212
Goodness-of-fit on F^2	1.031
Final R indices [I>2sigma(I)]	R1 = 0.0449 , wR2 = 0.1204
R indices (all data)	R1 = 0.0608 , wR2 = 0.1322
Largest diff. peak and hole	0.709 and -0.264 e.$Å^{-3}$

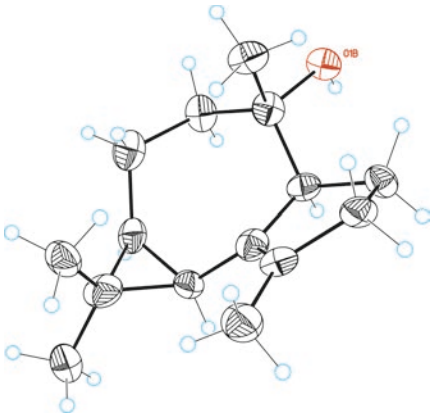


Table 2. Crystal data and structure refinement for **(4*R**)-4**.

Identification code	MLGLOB
Empirical formula	C15 H24 O
Formula weight	220.34
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 6.8966(4) Å
a= 90.00 °.	
	b = 46.307(3) Å
b = 98.017(2) °.	
	c = 12.7309(8) Å
g = 90.00 °.	
Volume	4026.1(4) Å^3
Z	12
Density (calculated)	1.091 Mg/m^3
Absorption coefficient	0.066 mm^{-1}
F(000)	1464
Crystal size	0.20 x 0.10 x 0.10 mm^3

Theta range for data collection	1.62 to 28.98 °.
Index ranges	-9 <=h<=7 ,-61 <=k<=45 ,-16 <=l<=16
Reflections collected	24804
Independent reflections	13158 [R(int) = 0.0427]
Completeness to theta =28.98 °	81.8%
Absorption correction	Empirical
Max. and min. transmission	0.9935 and 0.9870
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	13158 / 1713 / 1187
Goodness-of-fit on F^2	1.111
Final R indices [I>2sigma(I)]	R1 = 0.0659 , wR2 = 0.1717
R indices (all data)	R1 = 0.0885 , wR2 = 0.1953
Flack parameter	x =0.8(19)
Largest diff. peak and hole	0.318 and -0.289 e.$Å^{-3}$

UNIVERSITAT ROVIRA I VIRGILI
MECHANISTIC STUDIES ON GOLD MEDIATED CROSS-COUPLING REACTIONS AND TOTAL SYNTHESIS OF (_+)-EPIGLOBULOL
Madeleine Livendahl
Dipòsit Legal: T.1507-2013

Mechanistic Studies on Gold Mediated Cross-Coupling Reactions

Introduction

In synthetic organic chemistry much effort has been devoted to facilitating the construction of new C-C bonds. In 2010, this was demonstrated by awarding the fathers of palladium- catalyzed C-C bond forming reactions, Akira Suzuki, Richard F. Heck and Ei-ichi Negishi, the Nobel prize in chemistry.[1] The quest to find new ways of creating C-C bonds to construct more complex molecular structures is an ever-growing field in chemistry that continues to have a major impact in the literature.

The era of transition metal catalyzed bond forming reactions started in the sixties with a series of publications by Richard F. Heck for the successful coupling of phenyl palladium halides with ethylene.[2] Heck later perfected the method by incorporating the discovery made by Fitton in 1968.[3] The phenyl palladium intermediate had previously been generated by transmetalation between a Pd salt and an organomercury compound, but was now changed to oxidative addition of an organohalide and a Pd(0) source.[4] Heck's refined method is shown in Scheme 2.1, where the catalytic cycle starts with the active Pd(0) catalyst reacting with the organohalide in an oxidative addition. This alters the oxidation state of the palladium to Pd(II), forming an organopalladium intermediate, RPdX. In the next step,

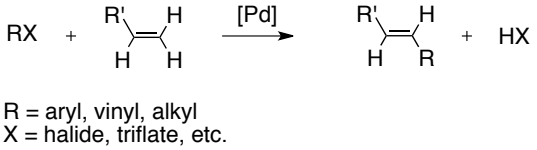
[1] "The Nobel Prize in Chemistry 2010 - Press Release". Nobelprize.org. 13 Apr 2013 http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/press.html

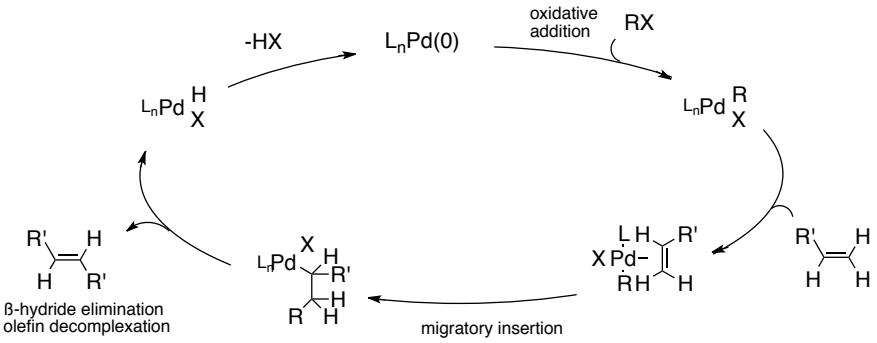
[2] (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518-5526. (b) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5526-5531. (c) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5531-5534. (d) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5538-5542. (e) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5542-5546.

[3] (a) Fitton, P.; McKeon, J. E. *Chem. Commun.* **1968**, *1*, 4-6. (b) Fitton, P.; McKeon, J. E. *Chem. Commun.* **1968**, *1*, 6-7.

[4] Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320-2322.

the olefin coordinates to palladium and the coordinated R group on the palladium migrates on to one of the carbons of the olefin while the palladium shifts on to the other carbon. This process is called a migratory insertion and results in the formation of a new C-C bond. The new olefin is released through a ß-hydride elimination and the palladium reenters the catalytic cycle as Pd(0) through the loss of HX.



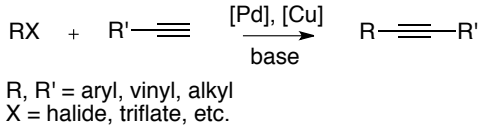


Scheme 2. 1. Mechanism of the Heck reaction.

Karasch,[5] Gilman,[6] Kumada,[7] and Murahashi[8] also investigated cross-coupling reactions using Grignard or organolithium compounds together with organohalides catalyzed by a transition metal. However, the highly reactive Grignard or organolithium reactants were not suitable for cross-coupling reactions due to their high reactivity, which often resulted in low

[5] Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316-2320.
[6] Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630-1634.
[7] Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4734-4736.
[8] Yamamura, M.; Moritani, I.; Murahashi, S.-I. *J. Organometal. Chem.* **1975**, *91*, C39-C42.

chemoselectivity and low tolerance for functional groups. However, palladium-catalyzed couplings have recently been developed using catalysts with bulky phosphines.[9] During the mid 1970's, two independent publications on cross-coupling of terminal alkynes together with vinyl- or aryl halides were published by the groups of Cassar[10] and Heck.[11] A few months later, Sonogashira[12] demonstrated that the reaction could be accelerated by the addition of Cu(I) salts as co-catalyst (scheme 2. 2).



Scheme 2. 2. Sonogashira cross-coupling reaction.

In 1977, Negishi published the successful coupling of an organohalide and an organozinc compound catalyzed by palladium.[13] The reaction was highly selective and gave superior yields compared to the earlier work using organometallic compounds. The reaction was also very mild and tolerant to a wide range of functional groups. Later development of this reaction has been made by, among others, the group of Knochel.[14] Negishi also discovered that an organoboron could be transmetalated to Pd, generating an active Pd species, which can be used in cross coupling reactions.

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[9] (a) Nagaki, A.; Kenmoku, A.; Moriwake, Y.; Hayashi, A.; Yoshida, J.-I. *Angew. Chem. Int. Ed.* **2010**, *49*, 7543-7547. (b) Giannerini, M.; Fañanás-Mastral, M.; Feringa, B. L. *Nat. Chem.* **2013**, *5*, 667-672.
[10] Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253-259.
[11] Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 259-263.
[12] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467-4470.
[13] (a) Negishi, E.-I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821-1823. (b) King. A. O.; Okukado, N.; Negishi, E.-I. *Chem. Commun.* **1977**, *19*, 683-684.
[14] Manolikakes, G.; Schade, M. A.; Muñoz Hernandez, C.; Mayr, H.; Knochel, P. *Org. Lett.* **2008**, *10*, 2765-2768.

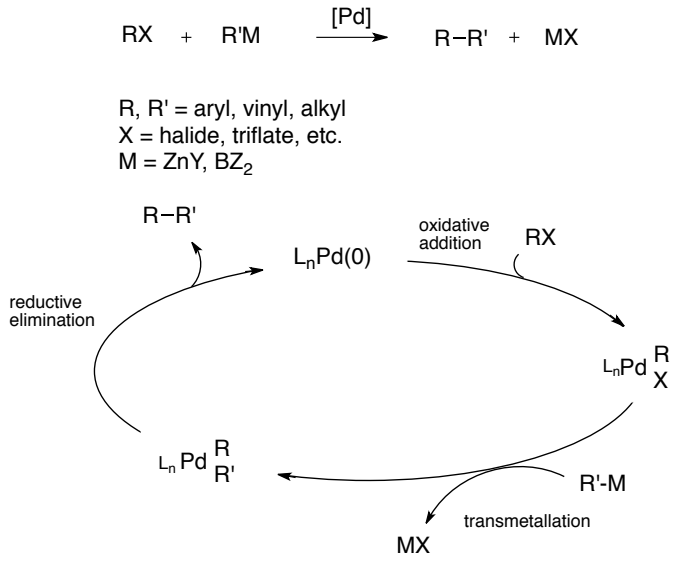
However, he did not pursue this discovery.[15] Instead, it was extensively investigated by the group of Suzuki, starting in 1979.[16] They found that an organoboron compound in the presence of base could be coupled to aryl and vinyl halides catalyzed by a Pd catalyst. Over the years the conditions of this reaction have been optimized to a very selective and mild procedure.

It was found by the group of professor Stille that organostannanes could be successfully coupled with acyl chlorides[17] and organohalides.[18] The reaction is highly versatile and mild, tolerant toward a wide range of functional groups, and the coupling partners are easily prepared.[19] This has led to it becoming one of the most used reactions for C-C bond formation. However, due to the high toxicity of organotin compounds its industrial use has been limited.

In the mechanism for the Stille, Suzuki and the Negishi cross-coupling reactions an organoboron or an organozinc compound, respectively, couples to an organohalide in the presence of catalytic amount of a Pd(0) source (scheme 2. 3). The first step is the oxidative addition of the aryl halide to the Pd(0) complex. This leads to the formation of an organometallic species, RPd(II)X, just as in the Heck reaction. In the second step the organogroup of an organostannane, organoboron or organozinc compound is transferred to the organopalladium intermediate through transmetalation, resulting in two organic groups coordinated to the palladium through

[15] Negishi, E.-I., "Selective Carbon-Carbon Bond Forming Reactions Mediated by Organozinc Reagents" in "Aspects of Mechanism and Organometallic Chemistry", Ed. J. H. Brewster, Plenum Press, New York, 1978, pp. 285-317.
[16] (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437-3440. (b) Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun.* **1979**, *19*, 866-867.
[17] Milstein, D.; Stille, J. K. *J. Am. Chem. Soc*. **1978**, *100*, 3636-3638.
[18] Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992-4998.
[19] Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, *25*, 508-524.

palladium-carbon bonds. These two groups are then coupled to each other through a reductive elimination, regenerating the reactive Pd(0) species.



Scheme 2. 3. Mechanism of the Negishi and Suzuki palladium-catalyzed cross-coupling reactions.

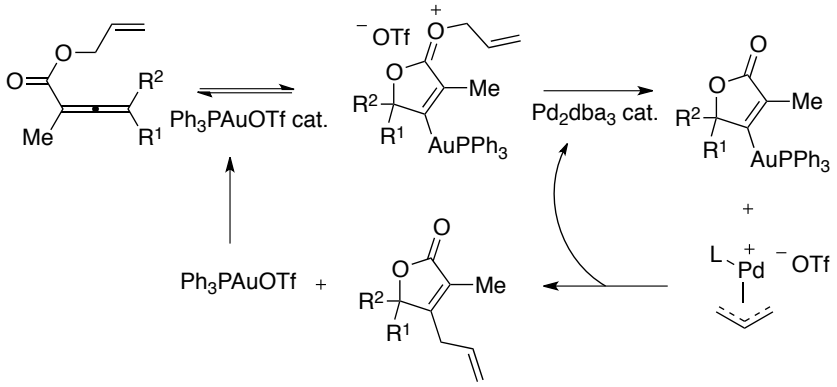
Bimetallic catalysis, such as in the Sonogashira reaction between palladium and copper, has led scientists to pursue new metal couples that are able to perform the Sonogashira reaction in a different or improved fashion. Gold and copper, both being group 11 elements, have been demonstrated to act in similar fashion in some catalytic reactions.[20] They both possess relatively

[20] See for example: (a) Huang, B.; Yao, X.; Li, C.-J. *Adv. Synth. Catal.* **2006**, *348*, 1528-1532. (b) Krause, N.; Aksin-Artok, Ö.; Breker, V.; Deutsch, C.; Gockel, B.; Poonoth, M.; Sawama, Y.; Sawama, Y.; Sun, T.; Winter, C. *Pure Appl. Chem.* **2010**, *82*, 1529-1536. (c) Hertwig, R. H.; Koch, W.; Schröder, D.; Schwarz, H.; Hrusák, J.; Schwerdtfeger, P. *J. Phys. Chem.* **1996**, *100*, 12253-12260. (d) Rasika Dias, H. V.; Flores, J. A.; Wu, J.; Kroll, P. *J. Am. Chem. Soc.* **2009**, *131*, 11249-11255. (e) Pérez-Galán, P.; Delpont, N.; Herrero-Gómez, E.; Maseras, F.; Echavarren, A. M. *Chem. Eur. J.* **2010**, *16*, 5324-5332.

high electronegativity and high Lewis acidity, albeit these features are more pronounced in gold. In fact, gold has been widely used in bimetallic catalysis together with other transition metals, especially in heterogeneous catalysis where gold can be applied as an alloy, a cluster, or as nanoparticles. [21] In homogeneous catalysis the most common metal combined with gold has been palladium, moreover there are also reports on several other metals being able to interact with gold in homogeneous catalytic systems (*vide infra*).

The group of Hashmi has published on dual metal catalysis involving Au and Pd. In these cases, gold is employed in stoichiometric amounts, acting as a transmetalating reagent to a Pd(II) catalyst.[22,24] One disadvantage of this method is the necessity of stoichiometric amounts of the gold complex, which is due to the difficulties to regenerate the organogold species. The group of Blum reported an oxidative cross-coupling process involving gold and palladium as catalysts where both were administered in substoichiometric amounts.[23] In the reaction these authors made use of the highly electron poor vinyl gold intermediate formed *in situ*, which successfully transmetalated with a Pd-allyl complex delivering the allylated product after reductive elimination (scheme 2. 4).

[21] Shah, A.; Rahman, L.; Qureshi, R.; Rehman, Z. *Rev. Adv. Mater. Sci.* **2012**, *30*, 133-149.
[22] (a) Hashmi, A. S. K.; Lothschütz, Döpp, R.; Rudolph, M.; Ramamurthi, T. D.; Rominger, F. *Angew. Chem. Int. Ed.* **2009**, *48*, 8243-8246. (b) Hashmi, A. S. K.; Ghanbari, M.; Rudolph, M.; Rominger F. *Chem. Eur. J.* **2012**, *18*, 8113-8119.
[23] Shi, Y.; Roth, K. E.; Ramgren, S. D.; Blum, S. A. *J. Am. Chem. Soc.* **2009**, *131*, 18022-18023.

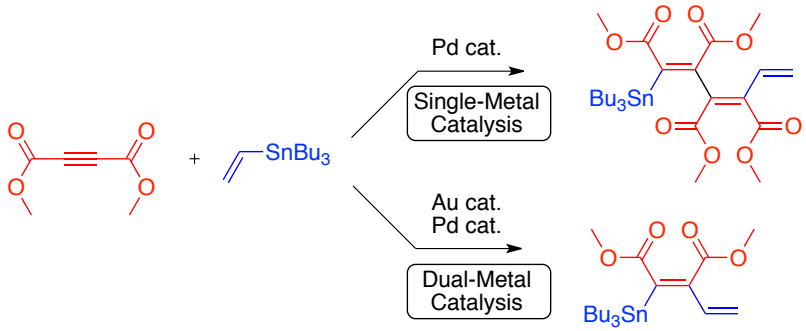


Scheme 2. 4. Au/Pd catalyzed butenolide rearrangement.

These results were later questioned by the group of Hashmi, investigating the possibility of Pd(0) as the sole catalyst.[24] The difficulties involving the use of both metals in catalytic amount stems from the competing proto-demetalation of gold, as well as from the regeneration of the reactive cationic organogold intermediate from the resulting L-Au-X complex normally formed in the catalytic cycle.

The group of Blum also performed a carbostannylation reaction of alkynes using palladium and gold as catalysts. They could demonstrate that when the reaction is catalyzed by Pd alone the double addition product was predominantly formed, whereas in the presence of gold as co-catalyst, the mono addition product was formed selectively (scheme 2. 5).[25]

[24] Hashmi, A. S. K.; Lotschütz, C.; Döpp, R.; Ackermann, M.; De Buck Becker, J.; Rudolph, M.; Scholz, C.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 133-147.
[25] Shi, Y.; Peterson, S. M.; Haberaecker, W. W.; Blum, S. A. *J. Am. Chem. Soc.* **2008**, *130*, 2168-2169.



Scheme 2. 5. Contrast between carbostannylation reaction catalyzed by palladium alone and a gold/palladium couple.

This possibility of transmetalation between gold and stannane was used by the group of professor Espinet which designed a Stille coupling using gold and palladium catalysts to cross-couple substrates known to be unreactive in these types of reactions.[26]

Other metals have also been used in dual catalysis with gold. There are examples of cross-coupling reactions using gold and nickel[27] as well as transmetalation of organic moieties from a gold complex to other metals such as rhodium,[28] iron[29, 30] and ruthenium.[29]

This way, gold-mediated catalysis has been diversified into the area of cross-coupling reactions. New areas of previously challenging cross-coupling reactions have been tackled with different novel designed gold catalysts together with other transition metal catalysts and have in many

[26] del Pozo, J.; Carrasco, D.; Pérez-Temprano, M. H.; García-Melchor, M.; Álvarez, R.; Casares, J. A.; Espinet, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 2189-2193.
[27] Hirner, J. J.; Blum, S. A. *Organometallics* **2011**, *30*, 1299–1302.
[28] Shi, Y.; Blum, S. A. *Organometallics* **2011**, *30*, 1776-1779.
[29] Contel, M.; Stol, M.; Casado, M. A.; van Klink, G. P. M.; Ellis, D. D.; Spek, A. L.; van Koten, G. A. *Organometallics* **2002**, *21*, 4556–4559.
[30] Hashmi, A. S. K.; Molinari, L. *Organometallics* **2011**, *30*, 3457-3460.

cases led to an enhancement of the reaction outcome.[31] This has surely inspired the various reports of cross-coupling transformations catalyzed by gold alone, for instance the gold-catalyzed Sonogashira reaction[32,33,34,35] and Suzuki[32,36,37] reaction. It has been argued that gold(I) complexes, having the same d^{10} configuration as Pd(0), could catalyze the reactions, typically mediated by palladium,[32,37] Albeit an interesting statement, the true nature of the active catalysts in most of these reactions has never been clarified. In fact, there are several other transition metals which readily form complexes with d^{10} electron configuration, such as Pt(0), but most of them are not able to catalyze the majority of transformations which readily can be carried out using palladium catalysts.[38] Thus, the electron configuration of the active transition metal species as crucial factor seems to be an oversimplification of the real complexity in catalysis.

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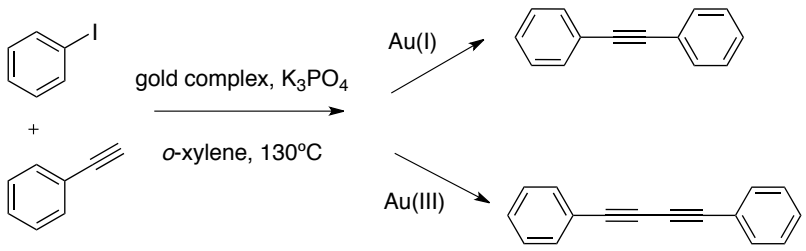
[31] Wegner, H. A.; Auzias, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 8236-8247.
[32] Plenio, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 6954-6956.
[33] (a) González-Arellano, C.; Abad, A.; Corma, A.; Garcia, H.; Iglesias, M.; Sánchez, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1536–1538. (b) Corma, A.; González-Arellano, C.; Iglesias, M.; Pérez-Ferreras, S.; Sánchez, F. *Synlett* **2007**, *11*, 1771–1774. (c) González-Arellano, C.; Corma, A.; Iglesias, M.; Sánchez, F. *Eur. J. Inorg. Chem.* **2008**, *11*, 1107–1115.
[34] Li, P.; Wang, L.; Wang, M.; You, F. *Eur. J. Org. Chem.* **2008**, *35*, 5946– 5951.
[35] de Souza, O. M. A.; Bittar, M. S.; Mendes, L. V. P.; Michele, C.; da Silva, F. *Synlett* **2008**, *12*, 1777–1780.
[36] Han, J.; Liu, Y.; Guo, R. *J. Am. Chem. Soc.* **2009**, *131*, 2060–2061.
[37] (a) Carrettin, S.; Corma, A.; Iglesias, M.; Sánchez, F. *Appl. Catal. A* **2005**, *291*, 247–252. (b) González-Arellano, C.; Corma, A.; Iglesias, M.; Sánchez, F. *J. Catal.* **2006**, *238*, 497–501. (c) Corma, A.; Gutiérrez-Puebla, E.; Iglesias, M.; Monge, A.; Pérez-Ferreras, S.; Sánchez, F. *Adv. Synth. Catal.* **2006**, *348*, 1899–1907. (d) Debono, N.; Iglesias, M.; Sánchez, F. *Adv. Synth. Catal.* **2007**, *349*, 2470–2476.
[38] See, for example: (a) Mateo, C.; Fernández-Rivas, C.; Cárdenas, D. J.; Echavarren, A. M. *Organometallics* **1998**, *17*, 3661–3669. (b) Nilsson, P.; Puxty, G.; Wendt, O. F. *Organometallics* **2006**, *25*, 1285–1292.

Objectives

It was our main objective during this project to fully characterize the different plausible catalytic cycles that could operate in a gold mediated cross-coupling reaction. We wanted to determine if gold could in fact act as the sole catalyst or if there were other catalytically active species that could play an active role in these transformations. We also wanted to further develop the study by theoretical calculations to gain access to the actual energy barriers that are present in gold mediated cross-coupling reactions.

Results

Reported palladium free Sonogashira reactions[39] (scheme 2. 6) prompted us to further investigate its mechanism in detail.



Scheme 2. 6. Sonogashira reaction catalyzed by gold complexes.

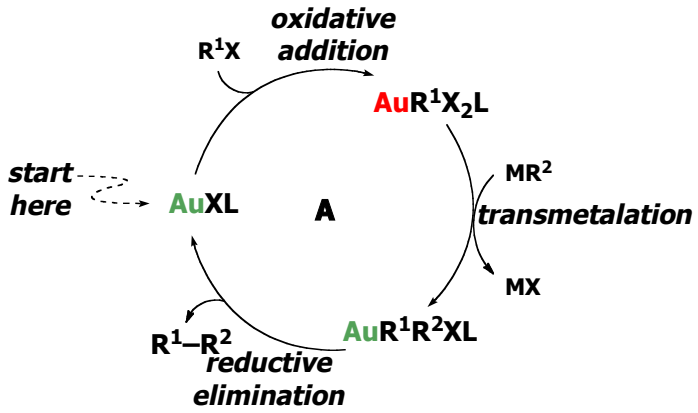
In earlier reports about cross-coupling reactions, gold catalysts often played the role of the transmetalating reagent, replacing either its counterpart copper, stannanes, and/or a boronic acid derivative (free acid or esters). However, in all cases gold has been applied in stoichiometric amounts and always together with another transition metal. Due to the known intrinsic reluctance of gold to change oxidation state we were surprised to see many reports where simple aryl halides had been used to oxidize gold(I) complexes into gold(III).[33b,33c,34,35,40] We therefore set out to duplicate every

[39] (a) González-Arellano, C.; Abad, A.; Corma, A.; Garcia, H.; Iglesias, M.; Sánchez, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1536–1538. (b) Li, P.; Wang, L.; Wang, M.; You, F. *Eur. J. Org. Chem.* **2008**, *35*, 5946-5941.

[40] See for example: (a) Shi, Y.; Roth, K. E.; Ramgren, S. D.; Blum, S. A. *J. Am. Chem. Soc.* **2009**, *131*, 18022-18023. (b) Plenio, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 6954-6956. (c) González-Arellano, C.; Abad, A.; Corma, A.; Garcia, H.; Iglesias, M.; Sánchez, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1536–1538. (d) Han, J.; Liu, Y.; Guo, R. *J. Am. Chem. Soc.* **2009**, *131*, 2060–2061. (e) Carrettin, S.; Corma, A.; Iglesias, M.; Sánchez, F. *Appl. Catal. A* **2005**, *291*, 247–252. (f) González-Arellano, C.; Corma, A.; Iglesias, M.; Sánchez, F. *J. Catal.* **2006**, *238*, 497–501. (g) Corma, A.; Gutiérrez-Puebla, E.; Iglesias, M.; Monge, A.; Pérez-Ferreras, S.; Sánchez, F. *Adv. Synth. Catal.* **2006**, *348*, 1899–1907. (h) Debono, N.; Iglesias, M.; Sánchez, F. *Adv. Synth. Catal.* **2007**, *349*, 2470–2476.

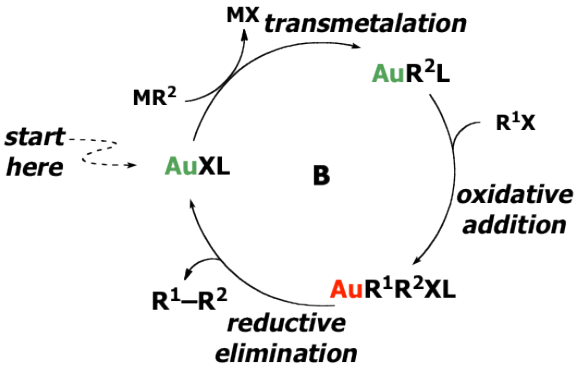
step of a plausible catalytic cycle of a cross-coupling reaction mediated solely by gold.

In contrast to palladium catalysis, gold can enter the catalytic cycle through two entry points. We can therefore draw two different catalytic cycles for gold. The first one is the classic cross-coupling pathway (scheme 2. 7) with the oxidative addition as the initial step oxidizing the gold(I) complex into a gold(III) complex. This step is then followed by a sigma bond metathesis with the corresponding transmetalating reagent, and thereafter a reductive elimination, regenerating the gold(I) species, to complete the cycle.



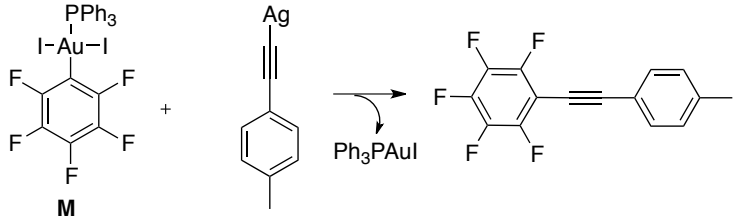
Scheme 2. 7. Classic cross-coupling reaction catalytic cycle

In the second catalytic cycle the gold(I) complexes transmetalates directly with the organometallic reagent MR^2 (scheme 2. 8). This intermediate would then undergo oxidative addition followed by reductive elimination just as in the previously described cycle.



Scheme 2. 8. Plausible catalytic cycle for Au in a cross-coupling reaction

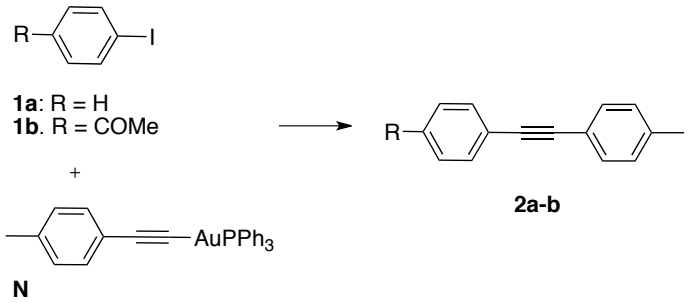
We confirmed the feasibility of the transmetalation step using a silver alkynyl complex, which indeed transferred its C-donor ligand to the Au(III) complex **M,** which is followed by reductive elimination of the two organic groups providing the expected product and the formation of Ph_3PAuI (scheme 2. 9).



*Scheme 2. 9. Transmetalation and reductive elimination on Au(III) complex **M**.*

The oxidative addition step, which was the more intriguing step of the catalytic cycle, was extensively studied. We chose triphenylphosphine gold chloride complex, and examined its reactivity with a number of different aryl halides. We followed the reactions closely by $^{31}P\{^{1}H\}$ NMR as well as by recrystallization of the crude reaction mixture. There was no indication in any of the experiments that any oxidative addition had taken place. In most cases, the only product isolated was the starting material, sometimes

together with the decomposed complex and Au(0). The possible reaction of a tolylacetylene complex **N** with two aryl halides was also attempted under various conditions, again without any signs of oxidative addition to the complex (table 2. 1).



Scheme 2. 10. Attempted oxidative addition to tolylacetylene complex N with aryl halides 1a and 1b.

Table 2. 1. Oxidative addition reactions of 1a-b under different conditions

Entry	1	Conditions	Additive	Yield (%)
1	**1a**	Toluene, 130ºC, 24h	-	<1%
2	**1a**	Toluene, 300ºC[a], 24h	-	<1%
3	**1a**	PhI as solvent, 30ºC, 24h	-	<1%
4	**1a**	Toluene, 130ºC, 24h	K_2CO_3	<1%
5	**1b**	Toluene, 130ºC, 24h	-	<1%
6	**1b**	Toluene, 130ºC, 16h	[Pd][b]	**2b** 100%

[a]Microwave heating. [b][Pd] = $[PdCl_2(PPh_3)_2]$ (1.4 mol%), *i*-Pr_2NH.

The authors of one of the papers on the successful Pd free Sonogashira coupling reported a gold complex with an unexpected structure, bearing three gold centers, all with different coordination to the ligand (complex **Y**, Figure 2. 1).[39] We decided to synthesize the same complex to verify whether this complex was indeed more active in this reaction.

The ligand is based on a mono imine-Schiff-base motif bearing also a fenolate and amide functionality. The synthesis was carried out from commercially available 3-*tert*-butyl-5-methylsalicylaldehyde and 1,1'-binaphtyl-2,2'-diamine, either as the monoimine or the diimine.

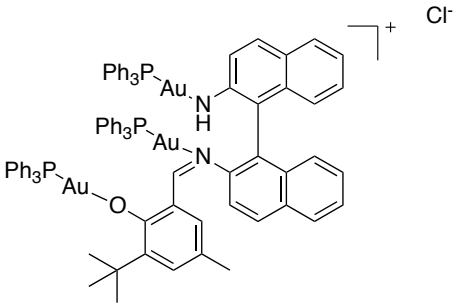


Figure 2. 1. Complex Y.

The authors of the paper[33a] kindly provided us with the ligand that they had used in the synthesis of the complex. However, this ligand was surprisingly found to be the diimine (**2**, figure 2. 2) and not the monoimine (**1**, figure 2. 2) as was stated in the paper. We were able to prepare both the mono- (**1**) and the diimine (**2**) by condensation of 3-*tert*-butyl-5-methylsalicyl aldehyde and 1,1'-binaphtyl-2,2'-diamine under acidic conditions in methanolic solutions. The monoimine (**1**) was isolated in 34% yield and the diimine (**2**) in 51%.

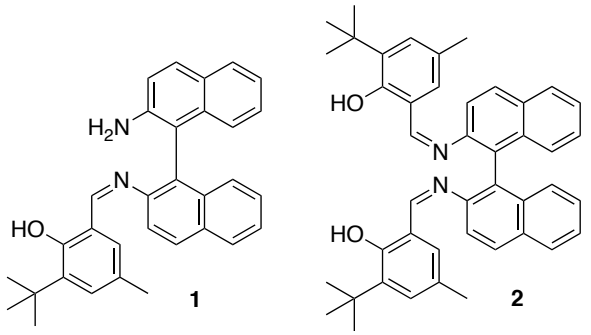
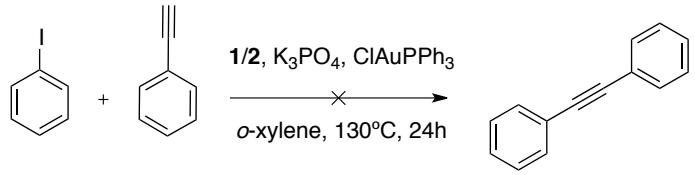


Figure 2. 2. Mono- and diimine Schiff base ligands

The ligand, K_3PO_4 and Ph_3PAuCl were dissolved in *o*-xylene in presence of iodobenzene and phenylacetylene at 130ºC for 24h (scheme 2. 11). The reaction mixture was then filtered through a pad of silica and the crude reaction mixture was concentrated and analyzed. No coupling product could be found, only unreacted starting material.



Scheme 2. 11. Failed cross coupling reaction of iodobenzene and phenyl acetylene.

Since Au(I) complexes with Au-O bonds are quite rare, as a comparison, we tested the same reaction as in scheme 2. 7 with a well characterized complex (**Z**)[41] (10 mol%) (figure 2. 3) in the presence of K_2CO_3 in toluene at 130ºC.[42] No sign of the cross-coupling product could be found, even in the presence of $Pd_2(dba)_3 \cdot CHCl_3$.

[41] Kolb, A.; Bissinger, P.; Schmidbauer, H. *Inorg. Chem.* **1993**, *32*, 5132–5135.
[42] Experiment performed by Dr. Torsten Lauterbach.

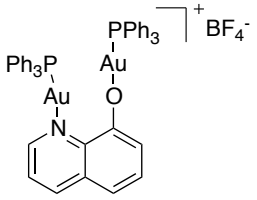


*Figure 2. 3. N, O-bonded gold(I) complex **Z**.*

A possible explanation of the reported successful coupling of many different acetylenes and aryl halides by gold catalysts can be trace amounts of palladium present in the system, which has acted as the real catalyst, thus gold merely acts as the transmetalating reagent. In agreement with this postulation we observed that some of the yields that were reported were quite low, even though using harsh reaction conditions and with large amounts of gold catalyst. To investigate this hypothesis, we prepared stock solutions of increasing amounts of $Pd_2(dba)_3 \cdot CHCl_3$ starting from 1.2 x 10^{-4} mol% up to 1.2 mol% (table 2. 2).[42]

Table 2. 2. Effect of Palladium on the Sonogashira Coupling with AuI/dppe[a]

Entry	[**Pd**][b] (mol%)	**Conversion** (%)	**Yield** (%)
1	-	<2%	<2%
2	1.2 x 10^{-4}	6	6
3	1.2 x 10^{-3}	16	16
4	1.2 x 10^{-2}	24	24
5	0.12	100	82
6	1.2	100	78
7[c]	1.2	<2%	<2%

[a] AuI (2 mol%), dppe (2 mol%), K_2CO_3, toluene, 130ºC, 16h.

[b] [Pd] = [$Pd_2(dba)_3 \cdot CHCl_3$]. [c] Room temperature.

We found that using concentrations as low as 1.2 x 10^{-2} mol% of the palladium catalyst gave yields superior to those reported with gold catalyzed reactions. We speculated, as it is known that even high purity gold often contains traces of palladium,[43] the active species in the reported palladium-free cross coupling reactions could in fact be due traces of palladium, either from an impure gold source or alternatively from small amounts of palladium still present in reaction vessels or on magnetic stirring bars. The gold iodide used in our experiments had a 3.1μg/g contamination of Pd, therefore being practically inactive as a catalyst in the Sonogashira reaction.

With these results in hand we concluded that it would be highly unlikely that gold is acting as a unique catalyst in these types of reactions and that the rate limiting step of the catalytic cycle is the oxidative addition step.[44]

So far we had only been investigating reported results regarding the gold catalyzed Sonogashira reactions, to acquire more in-depth knowledge of the feasibility of the change of oxidation state on a gold(I) center to gold(III) in a classic cross-coupling reaction setup we decided to further develop the topic after our own design. We asked ourselves, could we build a system where the oxidative addition would be so facilitated that we could surpass the energy barrier that seemed to be present? In order to understand exactly what this energy requirement is we initiated a collaboration with the group of Maseras (ICIQ) to attain theoretical calculations as well.

[43] Karadjova, I.; Arpadjan, S.; Jordanova, L. *Fresenius J. Anal. Chem.* **2000**, *367*, 146-150.
[44] Lauterbach, T.; Livendahl, M.; Rosellón, A.; Espinet, P.; Echavarren, A. M. *Org. Lett.* **2010**, *12*, 3006-3009.

Taking those observations in to account, we decided to design a ligand that would bear an aryl halide incorporated into its structure. This ligand would, upon coordination, place an aryl halide within 5 or 6 atoms from the gold center, making it feasible for an oxidative addition to occur intramolecularly and giving rise to a penta- or hexa-aura(III)cycle (figure 2. 4).

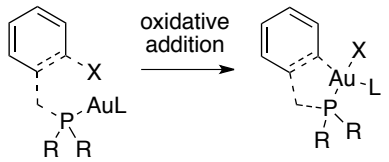
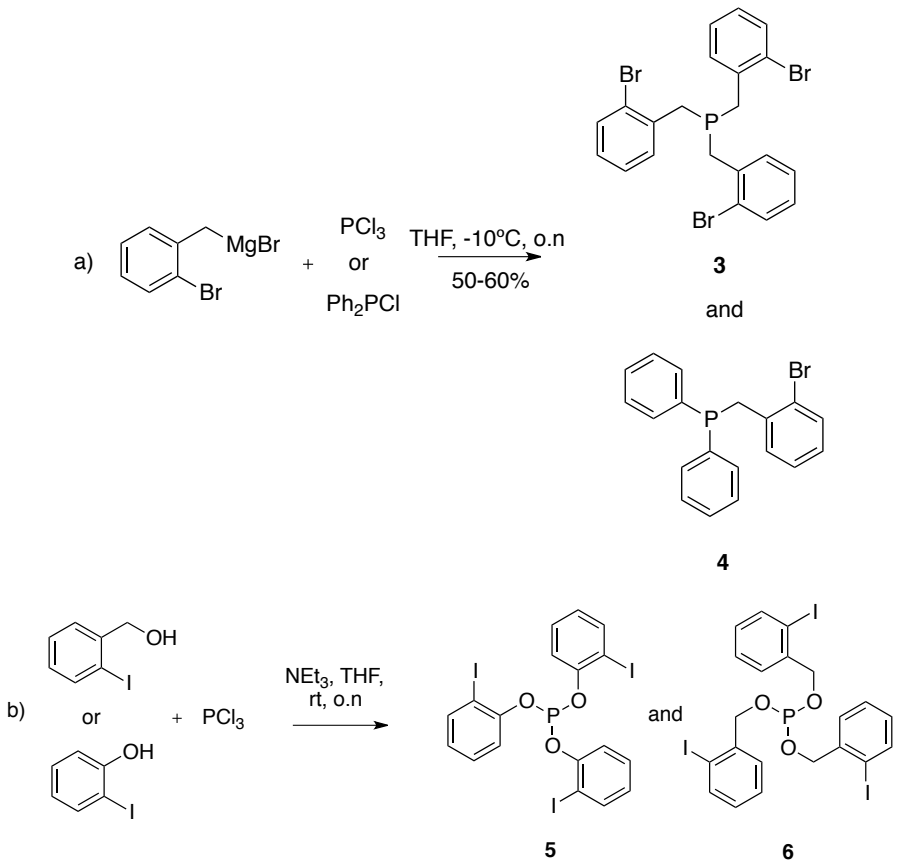


Figure 2. 4. New ligand design for possible intramolecular oxidative addition to Au(I) by aryl halide.

Since Au(III) prefers a square planar configuration we focused our efforts synthesizing the ligands that would give rise to five-membered metalacycles. Knowing that an oxidative addition more readily occurs to a metal with a high density of electrons,[45] we wanted to create complexes bearing ligands with pronounced σ-donor capacity such as phosphines and NHC carbenes. However, we also considered phosphites as ligands, due to their facile, straightforward synthesis. Both the phosphines as well as the phosphites were synthesized in one step procedures. The phosphine **3** was accessed through the reaction between PCl_3 and 2-bromobenzylmagnesium bromide (scheme 2. 12a) in good yield. The phosphites **5** and **6** were synthesized by reacting PCl_3 with 2-iodophenol or 2-iodobenzyl alcohol in presence of Et_3N (scheme 2. 12b). The (diphenyl)(aryl)phosphine (**4**) was synthesized starting from diphenylchlorophosphine and 2-bromobenzylmagnesium bromide (scheme 2. 12a).

[45] Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434-442.

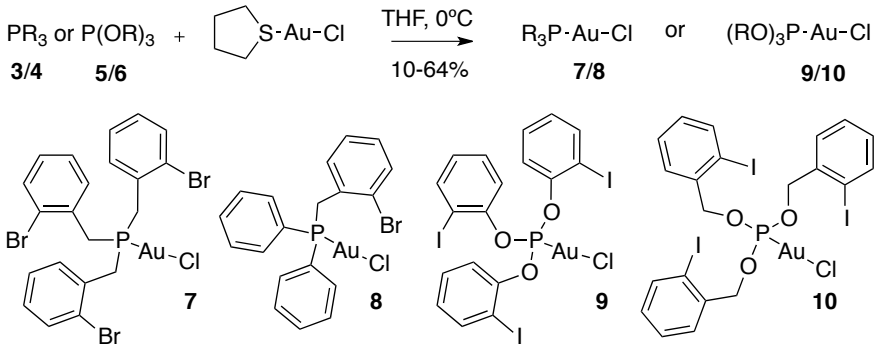


*Scheme 2. 12. Synthesis of phosphine and phosphite ligands **3**, **4**, **5** and **6**.*

All reactions were carried out under an inert atmosphere using degassed dry solvents. Tris(2-bromo-benzyl)phosphine (**3**) as well as the (2-bromobenzyl)diphenylphosphine (**4**) have been proven to be surprisingly air-sensitive compounds. They were therefore protected with BH_3 upon completion of the Grignard reaction. This gave air stable BH_3 coordinated phosphines that could be purified by column chromatography under non-inert conditions. The elimination of BH_3 was later done by dissolving the protected phosphines in degassed Et_2NH at 50ºC under Ar and the resulting pure phosphines were stored in the glove box.

The phosphites showed moderate stability but could never be completely purified as they readily hydrolyzed into their corresponding $(ArO)_2P(O)H$. It can easily be determined whether this happens by running a ^{31}P NMR analysis, which will show the characteristic doublet signal as a result of the P-H coupling, usually around 0-10 ppm.

The crude phosphites **5** and **6** and the pure phosphines **3** and **4** were all successfully coordinated to a gold(I) center upon their slow addition to a solution of tetrahydrothiophene gold chloride complex in CH_2Cl_2 at 0ºC (scheme 2. 13).



Scheme 2. 13. Synthesis of gold(I) complexes 7-10.

A cationic complex **11** was also formed with two equivalents of the tris-2-bromobenzyl phosphine (**3**). As this complex was nicely crystalline, we could show that this complex has six aryl halides around the gold center (figure 2. 5).

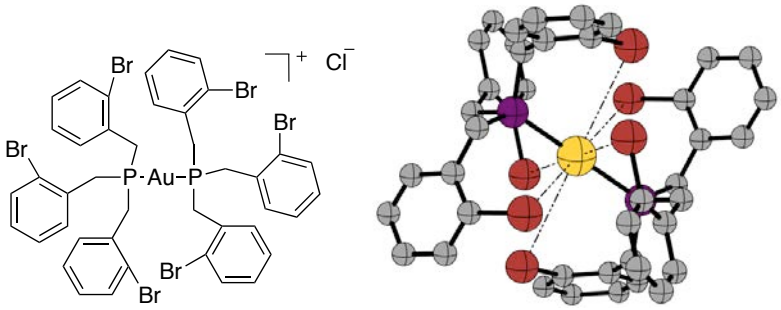
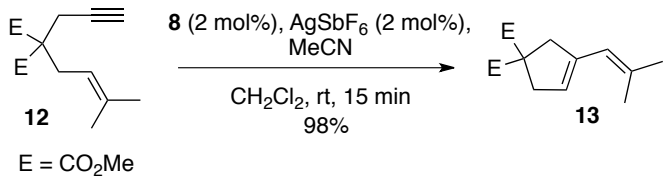


*Figure 2. 5. Cationic gold(I) complex **11** with ORTEP plot from its crystal structure*

The cationic complex derived from (2-bromobenzyl)diphenylphosphine gold chloride with benzonitrile as the labile ligand and hexafluoroantimonate as counterion was also synthesized *in situ* (**8**, scheme 2. 14). This complex was stable but highly active in the cyclization of 1,6-enynes (**12**, scheme 2. 14). The starting material was consumed in less than 15 min and gave high yield of the diene-product **13** as the result of a single cleavage skeletal rearrangement.

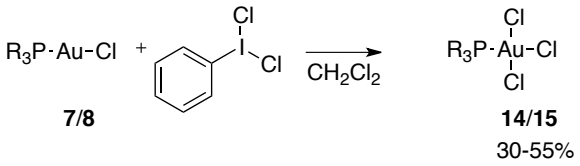


*Scheme 2. 14. Cycloisomerization reaction of enyne **12** catalyzed by gold complex **8**.*

With these newly synthesized complexes in hand we began a series of stability tests. Several harsh conditions were tried in order to force the intramolecular oxidative addition, such as refluxing the complex in different solvents for several days. However, it soon became clear that the complexes were very stable and unreactive towards an intra-molecular oxidative addition. Although one could imagine making the system even

more reactive by, for example, exchanging the bromide for an iodide or even a triflate, this proved difficult from a synthetic point of view.

As a confirmation that Au(III) complexes are stable and easily accessible complexes, **7** and **8** were oxidized using hypervalent iodine dichloroiodobenzene and the Au(III) trichloro complexes (**14-15**) were isolated as stable solids (scheme 2. 15).



7/8 **14/15** 30-55%

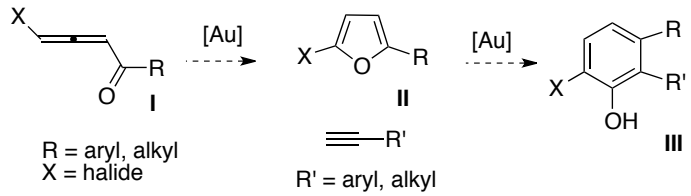
*Scheme 2. 15. Oxidation of Au(I) complexes 7 and **8** by dichloroiodobenzene.*

It is important to note that despite the fact that the model complexes have been proved to be unreactive towards oxidative addition, it does not mean that they are inert in classic gold catalyzed transformations, as it is demonstrated by the successful cycloisomerization of enyne **12** (scheme 2. 14). They are also susceptible to oxidation into Au(III) when employing a strong oxidant such as a hypervalent iodine reagent.

This type of oxidative stability towards C_{sp^2}-X bonds could help to construct coupling partners suitable in catalysis with other transition metals. Aryl halides are important building-blocks in total synthesis as they often are coupling partners in C-C bond forming reactions.[46] However, the synthesis of highly substituted aryl halides often requires harsh reaction

[46] Nicolau, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489.

conditions and the use of toxic halogenating reagents.[47] As an alternative one could envision cyclizations of halide substituted allenes (**I**) by a gold source, resulting into the formation of a substituted furan bearing a halide (**II**).[48] This furan could then be used in a reaction resembling the phenol synthesis developed by the group of Hashmi[49] where the final product would be a densely functionalized aryl halide **III** (scheme 2. 16).



Scheme 2. 16. Possible synthetic route towards phenol-halides using gold catalysis.

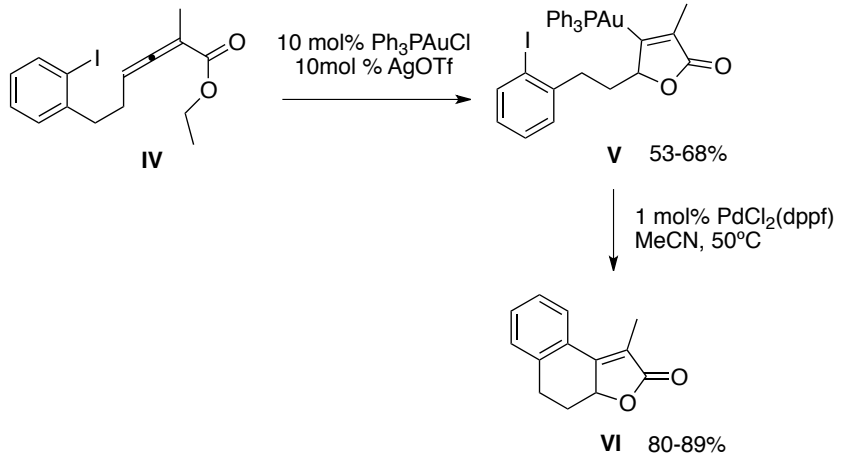
In fact, the group of Hashmi has taken advantage of this redox stability in the synthesis of a bicyclic intermediate **V** later used in a cross-coupling reaction together with a palladium catalyst (Scheme 2. 17).[50]

[47] (a) Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, P. V. *Synthesis* **2007**, *16*, 2534-2538. (b) Rajesh, K.; Somasundaram, M.; Saiganesh, R.; Balasubramanian, K. K. *J. Org. Chem.* **2007**, *72*, 5867-5869. (c) Surya Prakash, G. K.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770-15776.

[48] Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500-10501.

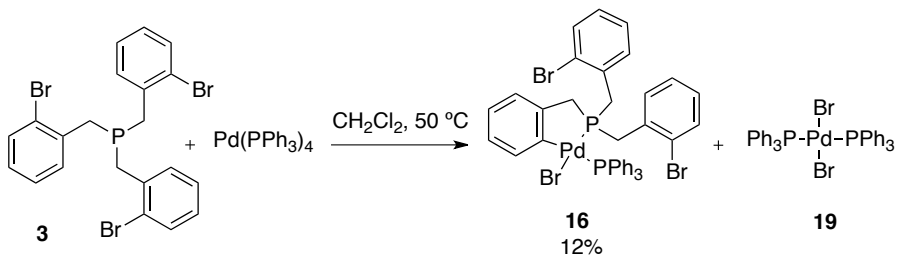
[49] Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769-3771.

[50] Hashmi, A. S. K.; Lotschütz, C.; Döpp, R.; Ackermann, M.; De Buck Becker, J.; Rudolph, M.; Scholz, C.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 133-147.



*Scheme 2. 17. Catalytic cycloisomerization using a Au(I) catalyst of an allene compound (**IV**) bearing aryl halide.*

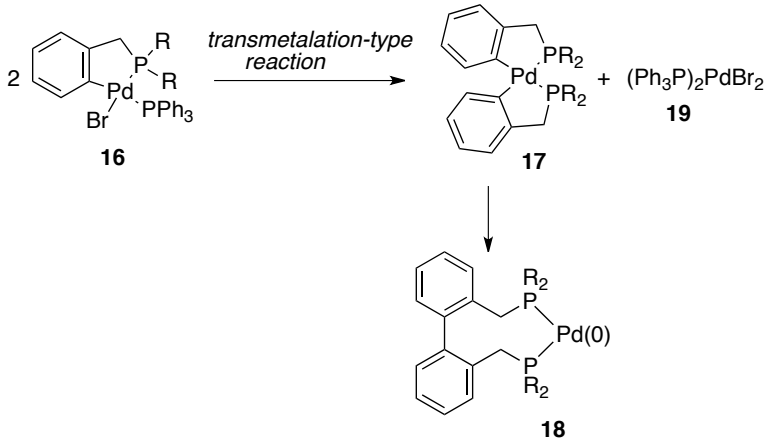
For comparison, a palladium complex bearing the tris-2-bromo-benzyl phosphine (**3**) was synthesized and heated to 50 ºC over night to induce the oxidative addition. Palladacycle (**16**) could be isolated in 12% yield (scheme 2. 18).



*Scheme 2. 18. Synthesis of palladacycle **16**.*

Although the reaction occurred readily, the palladacycle **16** was only isolated in low yield. In addition, Pd(II) complex **19** precipitated out of the reaction mixture in large amounts. The formation of complex **19** can be explained by the decomposition of palladacycle **16** in a transmetalation-type reaction resulting in complexes **17** and **19**. Complex **17** can then

reductively eliminate forming complex **18**, or related species (scheme 2. 19).



*Scheme 2. 19. Formation of Pd complexes **17** and **19**.*

Theoretical calculations

The calculations performed by Charles Goehry in the group of Prof. Maseras (ICIQ) provided information that was in accordance with the data obtained experimentally. The energy requirements for the oxidative addition of an aryl halide to triphenylphosphine gold chloride showed prohibitively high barriers reaching up to 43 kcal/mol for the transition states (table 2. 3). This is in line with the observed high redox potential of the Au(I)/Au(III) couple ($E^0 = +1.41V$).[51]

[51] Bratsch, S. G. *J. Phys. Chem. Ref. Data* **1989**, *18*, 1-21.

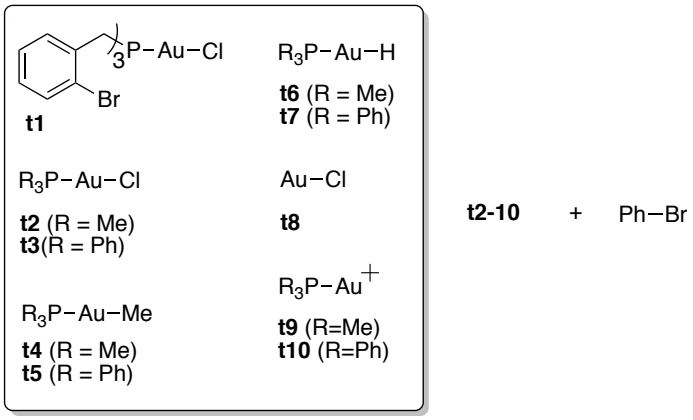


Figure 2. 6. Computed reactants.

Table 2. 3. DFT calculations with the M06 functional (C, H, P, Cl) and SDD (Au).

Reacted system	TS	Product
t1	41.5	17.4
t2	42.6	36.5
t3	43.0	36.4
t4	47.3	4.1
t5	46.8	6.5
t6	48.5	5.2
t7	45.3	7.5
t8	11.7	4.5
t9	23.3	12.1
t10	21.6	12.7

The intramolecular setup (**t1**) based on complex **7** in the experimental work, was tested to verify the lack of reactivity that had been observed experimentally. A transition state was found lying at 41.5 kcal/mol, which is prohibitively high for the oxidative addition in a catalytic reaction under normal reaction conditions. A cause for this high-lying transition state was thought to come from the *trans* relationship formed in between the incoming phenyl bromide and the product (see **t1ts** in figure 2. 7).

Other gold complexes were computed bearing phosphine ligands with different ligands (**t2-t10**). All model complexes were computed as reactants in an oxidative addition reaction with phenyl bromide. As is shown in the table the computed systems are hardly affected by the difference in ligands: chloro (**t2-t3**), methyl (**t4-t5**) and hydride (**t6-t7**) all give prohibitively high transition states when bearing phosphine ligands. Cationic model complexes **t9** and **t10** also exhibit high-lying TS, albeit at a somewhat lower level. Monocoordinated complex **t8** show a lower-lying transition state. This could have an explanation in the well known preference for a linear 2-coordinated coordination of Au(I) complexes.[52] This favored coordination is challenged upon the formation of the two new bonds in the transition state for complexes already bearing two ligands, which could explain the lowering of the barriers seen in **t8-t10**. This indicates that the 2-coordination plays a role in the energetic constraints of the reaction. However, this only serves as an interpretation tool since experimentally these types of monocoordinated complexes are hardly accessible. One can also see that the high-lying transition state seen with **t1** thought to be due to the *trans*-nature of the intermediate has an almost identical entropy penalty

[52] Although the majority of Au(I) complexes are two-coordinated, linear 14-electron species, three- and four-coordinated Au(I) complexes are also known: Gimeno, M. C.; Laguna, A. *Chem. Rev.* **1997**, *97*, 511–522.

as when bringing two different molecules together. This ultimately means that it is not the intramolecular nature of the experimental setup that affects the reaction outcome but rather that these systems demonstrate an intrinsic reluctance to undergo oxidative addition.

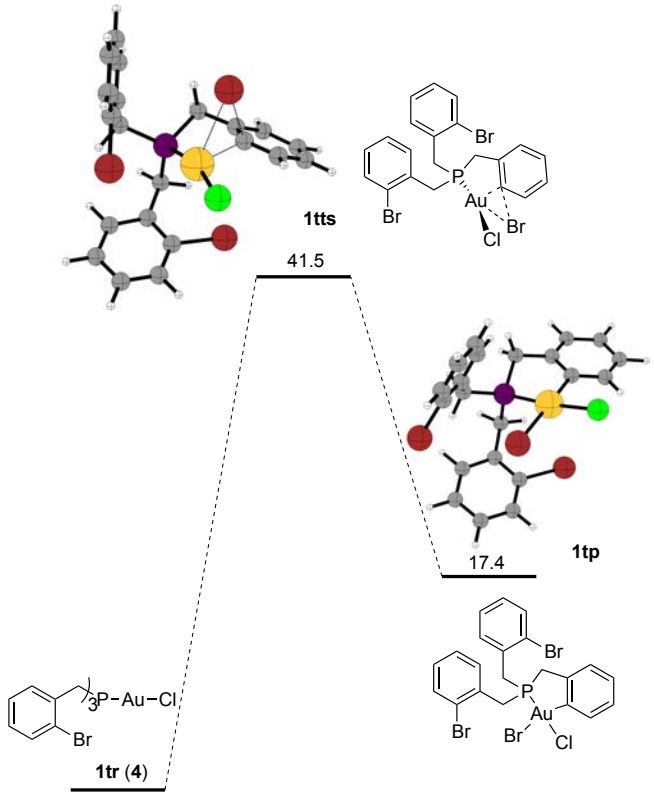


Figure 2. 7. Transition states for the intramolecular oxidative addition by aryl halide on to Au(I).

Further calculations showed as well that the more electron depleted the aryl halide was rendered, the lower the barrier for the oxidative addition became (table 2. 4). When substituting the aryl bromide ring with electron withdrawing substituents such as nitrile or nitro the transition state becomes in some cases significantly lower lying than when using simple phenyl bromide. When substituted in *ortho*, *ortho* and *para* positions with NO_2 and CN the transition state lies roughly 10 kcal/mol lower than when not. Electron-donating groups such as amino shows much less effect when

varying the positions on the aryl ring. The transition state lies in all cases at a prohibitively high level.

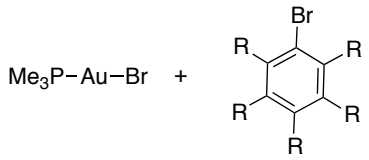


Figure 2. 8. Computed reactants for oxidative addition of densely functionalized aryl halide to Au(I) complex.

Table 2. 4. Effects of substitutional patterns on aryl bromide. Computed M06 Relative Energies (kcal·mol^{-1}) of transition states for oxidative addition.

Substitution	**CN**	**NH_2**	**NO_2**	**H**
none				42.4
ortho	40.3	40.8	36.9	
ortho-ortho	39.0	41.1	31.9	
meta	42.7	41.8	45.2	
meta-meta	42.8	41.6	43.5	
para	41.4	41.7	40.6	
all positions	34.2	40.1	31.7	
ortho-ortho-para	35.8	40.6	28.0	

These results give a clear indication that the transition state of the oxidative addition of any aryl halide to a gold chloride complex lies too high for a catalytic reaction under normal conditions. Analogously, when computing the transition state for the oxidative addition on palladacycle **16,** it lies at a much lower level and the reaction proceeds as expected (figure 2. 9). Stronger oxidants such as bromine and chlorine also give a lower lying transition state for the addition to Me_3PAuBr (figure 2. 9), while methyl

iodide also show a high-lying transition state towards the same Au(I) complex. This is a clear indication that under the usual conditions of the Sonogashira cross-coupling reaction, applying gold complexes as catalysts, the rate limiting step of the reaction will be the oxidative addition of aryl halides to the Au(I) complex. This impediment cannot be omitted by the use of highly reactive reagents such as aryl iodides, or with an intramolecular setup.

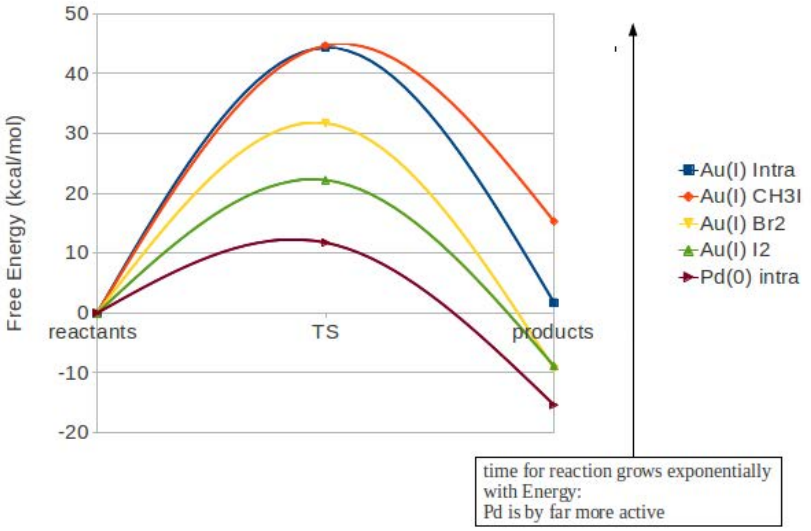
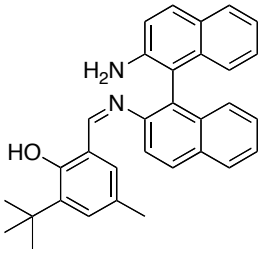


Figure 2. 9. Barriers for transition states of oxidation of gold and palladium complexes with different oxidants.

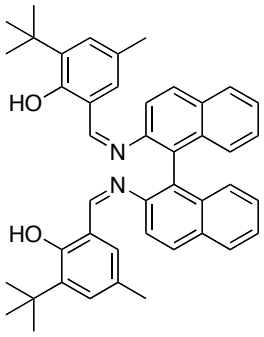
Conclusions

We have investigated two plausible catalytic cycles in which gold could act as the unique catalyst in a classic cross-coupling reaction. After extensive experimental studies we concluded that the probability of gold as the sole acting catalyst in these reactions was highly unlikely. Our experiments pointed to the oxidative addition step as the rate-determining. This is in accordance with the known intrinsic reluctance of gold(I) to change oxidation state. We continued our studies in collaboration with the theoretical group of prof. Maseras (ICIQ) to calculate the activation energy of the hypothetical oxidative addition step in a classic cross-coupling reaction setup. These values were shown to be prohibitively high (ca 40 kcal/mol). As an investigation of the limits of this high activation barrier we designed a gold complex that intramolecularly could undergo an oxidative addition. We wanted to see if we could provoke the reaction to occur if put under the most advantageous conditions. However, in all cases the complexes were proven unreactive towards their intramolecular reactions. As a comparison the analogous palladium complex was synthesized and the resulting palladacycle formed from the intramolecular oxidative addition was isolated. These results show that albeit both being transition metals with a d^{10} configuration, palladium and gold are highly differentiated in a classic catalytic cross-coupling reaction. The use of gold as the sole catalyst in these types of transformations therefore would require a stronger oxidant than the aryl halides normally employed.

Experimental part



2-(((2'-amino-[1,1'-binaphthalen] -2-yl)imino)methyl) -6- (*tert*-butyl)-4-methylphenol (1): 3-*tert*-Butyl-5-methylsalicylaldehyde (0.225 g, 1.17 mmol) in absolute ethanol was added to a solution of 1,1-binaphtyl-2,2-diamine (1.00 g, 3.52 mmol) in absolute ethanol (100 ml). Glacial acetic acid (4 mL) was then added and the solution was heated to reflux until the aldehyde had been consumed (TLC). The crude reaction mixture was then filtered through a silica plug and the resulting liquid was concentrated under reduced pressure. The crude solid was purified by chromatography (5-10% EtOAc in hexane) on silica saturated with triethylamine to give mono-imine **10** (184.1 mg, 34%) as a beige colored foam-solid, mp 92-96 ºC. ^{1}H NMR (400 MHz, CD_2Cl_2) δ = 8.64 (s, 1H), 8.09 (d, J = 8.9 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 8.9 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.9 Hz, 1H), 7.50 (t, J = 8.2 Hz, 1H), 7.40-7.32 (m, 2H), 7.19-7.10 (m, 3H), 7.05 (d, J = 2.0 Hz, 1H), 6.90 (d, J = 1.6 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 3.67 (bs, 2H), 2.21 (s, 3H), 1.20 (s, 9H). ^{13}C NMR (101 MHz, CD_2Cl_2, DEPT) δ 163.0 (CH), 158.5 (C), 144.8 (C), 142.6 (C), 137.4 (C), 134.3 (C), 133.6 (C), 133.2 (C), 131.7 (CH), 130.5 (CH), 130.2 (CH), 129.6 (CH), 128.6 (CH), 128.6 (C), 128.4 (CH), 128.2 (C), 127.4 (CH) 127.1 (C), 126.7 (CH), 126.5 (CH), 126.3 (CH), 124.1 (CH), 122.3 (CH), 118.9 (C), 118.4 (CH), 118.3 (CH), 114.3 (C), 34.8 (C), 29.2 (3xCH_3), 20.6 (CH_3). IR (Diamond): 3378-3471 (NH_2), 1577 (C=N) cm^{-1}. MS-ESI: *m/z* for $C_{32}H_{30}N_2O$ found 459.1 $[M+1]^+$. $C_{32}H_{30}N_2O \cdot 0.5H_2O$: calcd C 82.19, H 6.68, N 5.99: found C 82.50, H 6.78, N 5.96.

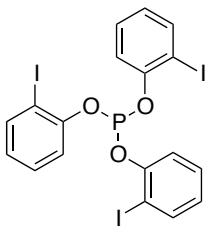


([1,1'-binaphthalene]-2,2'-diylbis (azanylylidene))bis(methanylylidene))bis(2-(*tert*-butyl)-4-methylphenol) (2): 1,1-Binaphtyl-2,2-diamine (166 mg, 0.58 mmol), 3-*tert*-butyl-5-methylsalicylaldehyde (0.225 g, 1.17 mmol) and glacial acetic acid (4 mL) were dissolved in absolute ethanol (100 mL) and the solution was heated to reflux until no more starting material could be seen (TLC). The crude reaction mixture was then filtered through a silica plug and the resulting liquid was concentrated under reduced pressure. The crude solid was purified by chromatography (10% EtOAc in hexane) on silica saturated with triethylamine to give diimine **11** (188.1 mg, 51%) as an orange colored foam-solid, mp 228-229 ºC. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.55 (s, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.48-7.44 (m, 1H), 7.31-7.29 (m, 2H), 7.03 (d, J = 1.9 Hz, 1H), 6.79 (d, J = 1.6 Hz, 1H), 2.18 (s, 3H), 1.20 (s, 9H). ^{13}C NMR (101 MHz, CD_2Cl_2, DEPTQ) δ 163.3 (CH), 158.4 (C), 144.6 (C), 137.2 (C), 133.7 (C), 132.9 (C), 131.5 (CH), 130.5 (CH), 130.2 (CH), 129.3 (C), 128.5 (CH), 127.1 (CH), 127.0 (C), 126.8 (CH), 125.9 (CH), 119.0 (C) 117.7 (CH), 34.8 (C), 29.2 (3xCH_3), 20.6 (CH_3). IR (Diamond): 1577 (C=N) cm^{-1}. HRMS-ESI: *m/z* calcd for $C_{44}H_{44}N_2O_2$: 631.3325; found 633.3352 $[M+1]^+$.

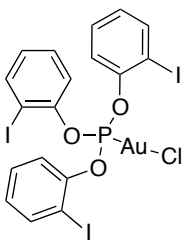
Sonogashira coupling

A mixture of phenylacetylene (1.5 equiv), phenyl iodide (1 equiv), the crude Au-complex formed from potassium salts of either **1** or **2** and [AuClPPh$_3$] (0.2 equiv) and K_3PO_4 (2 equiv) were dissolved in *o*-xylene (3 mL) in a 10 mL Schlenk tube. The reaction was heated to 130ºC for 24 h. After cooling down, the mixture was filtered through a pad of silica (hexanes/EtOAc) and the solvent was evaporated. The resulting mixture

was analyzed by GC-MS as well as ^{1}H-NMR and ^{13}C-NMR. No coupled product was detected.



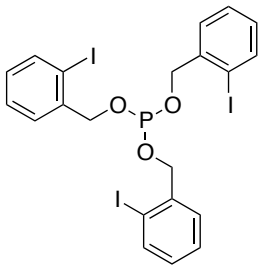
Tris(2-iodophenyl)phosphite (5): Using a syringe pump, Et_3N (1.26 mL, 9.10 mmol) was added to a solution of 2-iodophenol (2.00 g, 9.10 mmol) and PCl_3 (265 μL, 3.00 mmol) in dry THF (15 mL) in a Schlenck flask under strictly inert conditions. The solution was stirred at room temperature for 24 h. After making sure that all PCl_3 had been consumed (^{31}P NMR) the solution was filtered under a flow of Ar over a pad of silica. The filtrate was quickly evaporated on a rotavap connected to the Ar line and the resulting gray oil was dried over night under high vacuum and then transferred into the glove box. The phosphite ligand was used without further purification. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.85 (dd, J = 7.9, 1.5 Hz, 1H), 7.39 (m, 1H), 7.34 (m, 1H), 6.91 (m, 1H). ^{31}P NMR (202 MHz, CD_2Cl_2) δ 132.7 (s).



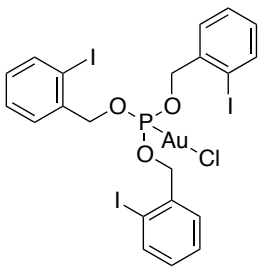
Chloro[tris(2-iodophenyl)phosphite] gold (9):[53] A dry tube containing chloro(tetrahydrothiophene) gold (205 mg, 0.64 mmol) was transferred into the glove-box. To the tube was added tris(2-iodophenyl)phosphite (**5**) (1.3 mL, 1.46 M stock solution in CH_2Cl_2). After stirring for 30 min the tube was taken out of the glove box and the solution was concentrated by rotary evaporation. The complex was then purified by column chromatography (83% CH_2Cl_2 in cyclohexane) to give the pure complex as a snow-white solid (102 mg, 17%). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.93 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.12 – 7.04 (m, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 149.9

[53] Hashmi, A. S. K.; Loos, A.; Littmann, A.; Braun, I.; Knight, J.; Doherty, S.; Rominger, F. *Adv. Synth. Catal.* ***2009****, 351, 576-582.*

(C), 140.9 (CH), 130.5 (CH), 128.8 (CH), 123.1 (CH), 90.2 (C). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 116.59 (s). HRMS-ESI: *m/z* calcd for $C_{18}H_{12}AuClI_3O_3P$: 942.6910; found 942.6865 $[M+]Na^+$. $C_{18}H_{12}AuClI_3O_3P$: calcd C 23.49, H 1.31, N 0: found C 23.74, H 1.49, N 0.05.

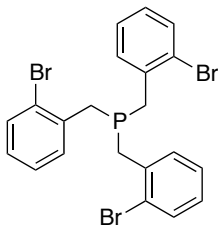


Tris(2-iodobenzyl)phosphite (6): Using a syringe pump, Et_3N (1.20 mL, 8.30 mmol) was added to a solution of 2-iodobenzyl alcohol (2.00 g, 8.30 mmol,) and PCl_3 (250 μL, 2.80 mmol) in dry THF (15 mL) in a Schlenck flask under strictly inert conditions. The solution was stirred at room temperature for 24 h. After making sure that all PCl_3 had been consumed (^{31}P NMR) the solution was filtered under a flow of Ar over a pad of silica. The filtrate was quickly evaporated on a rotavap connected to the Ar line and the resulting gray oil was dried over-night under high vacuum and then transferred into the glove box. The phosphite ligand was used without further purification. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.83 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 4.95 (d, J = 7.3 Hz, 2H). ^{31}P NMR (202 MHz, CD_2Cl_2) δ 143.10 (s). HRMS-ESI: *m/z* calcd for $C_{21}H_{19}I_3O_3P$: 730.8200; found 730.8203 [M+H].



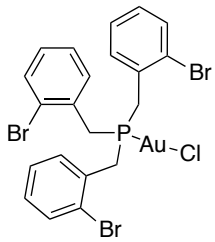
Chloro[tris(2-iodobenzyl)phosphite] gold (10):[53] A dry tube containing the chloro(tetrahydrothiophene) gold (221 mg, 0.70 mmol) was transferred into the glove box and dissolved in dry CH_2Cl_2 (0.5 mL). To the tube was added tris(2-iodobenzyl)phosphite (507 mg, 0,70 mmol) (**6**) in CH_2Cl_2 (0.5 mL). After stirring for 30 min the tube was taken out of the glove box and the solution was concentrated by rotary

evaporation. The complex was then purified by column chromatography (50% CH_2Cl_2 in cyclohexane) to give the pure complex as a snow-white solid (60 mg, 10%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.86 (d, J = 7.9 Hz, 1H), 7.38 (m, 2H), 7.11–7.02 (t, J = 7.6 Hz 1H), 5.17 (d, J = 9.8 Hz, 2H).^{13}C NMR (126 MHz, CD_2Cl_2) δ 140.1 (CH), 137.4 (C), 130.6 (CH), 129.9 (CH), 128.6 (CH), 98.6 (C), 73.2 (CH2). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 121.91 (s). HRMS-ESI: *m/z* calcd for $C_{21}H_{18}AuClI_3O_3P$: 984.7380; found 984.7311 $[M+]Na^+$. $C_{21}H_{18}AuClI_3O_3P$: calcd C 26.21, H 1.89, N 0: found C 26.80, H 2.04, N 0.07.

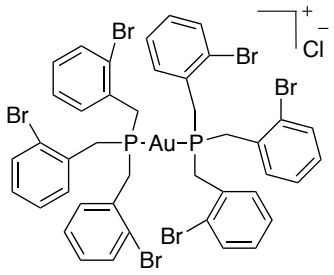


Tris(2-bromobenzyl)phosphine (3): PCl_3 (142 μL, 1.60 mmol) was added dropwise to a solution of 2-bromobenzyl magnesium bromide (20 mL, 5.00 mmol, 0.25 M in THF) in dry THF (20 mL) in a Schlenck flask under strictly inert conditions at -10ºC. The septum of the Schlenck flask was carefully covered with parafilm and the key to the argon line was closed. When at room temperature the ice-bath was removed and the solution was left stirring in this manner over night. After making sure that all PCl_3 had been consumed (^{31}P-NMR) the solution was cooled down to 0ºC and BH_3·THF complex (15 mL, 15.0 mmol, 1M in THF) was added. The solution was left stirring until it reached room temperature and all phosphine had been protected (^{31}P-NMR), normally 2 h. The reaction was carefully quenched by the slow addition of H_2O at 0ºC. The two organic phases were separated and the aqueous phase was washed once with EtOAc. The organic fractions were combined, dried and concentrated onto Florisil. The concentrated product was then purified by column chromatography (3% EtOAc in cyclohexane) and the purified protected phosphine was transferred into a dried flask. Degassed Et_2NH was added and the solution was stirred for 3h at 50ºC or until all phosphine had been deprotected. The excess amine was removed by inert evaporation

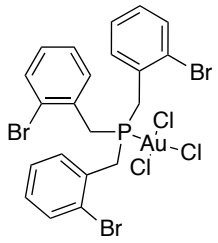
and the resulting oil was dissolved in dry degassed CH_2Cl_2 and transferred into a tarred Schlenck and the solution was concentrated. The pure phosphine was then transferred for storage to the glove box (520 mg, 60%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.15 (m, 2H), 7.03 (m, 1H), 3.14 (s, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 138.29 (d, *J* = 6.9 Hz, C), 133.27 (CH), 131.34 (d, *J* = 7.4 Hz, CH), 127.98 (d, *J* = 2.8 Hz, CH), 127.79 (CH), 125.00 (d, *J* = 4.1 Hz, C), 35.41 (d, *J* = 21.7 Hz, CH_2). ^{31}P NMR (162 MHz, CD_2Cl_2) δ -6.32 (s). HRMS-ESI: *m/z* calcd for $C_{21}H_{19}Br_3P$: 538.8769; found 538.8783.



Chloro[tris(2-bromobenzyl)phosphine] gold (7):[53] A dry tube containing the chloro(tetrahydrothiophene) gold (100 mg, 0.30 mmol) was transferred into the glove box and dissolved in dry CH_2Cl_2 (0.5 mL). To the tube was added tris(2-bromobenzyl)phosphine (**3**) (170 mg, 0.30 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 30 min the tube was taken out of the glove box and the solution was concentrated by rotary evaporation. The complex was then purified by column chromatography (50% CH_2Cl_2 in cyclohexane) to give the pure complex as a snow-white solid (115 mg, 50%). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.46 (dt, *J* = 7.7, 1.9 Hz, 1H), 7.33 (t, *J* = 8.0, 1H), 7.21 (tt, *J* = 8.0, 1.9 Hz, 1H), 3.65 (d, *J* = 11.4 Hz, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 133.9 (CH), 133.1 (C), 132.3 (CH), 129.9 (CH), 128.6 (CH), 125.5 (C), 33.6 (CH_2). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 40.39 (s). HRMS-ESI: *m/z* calcd for $C_{21}H_{18}AuClBr_3P$: 734.8362; found 734.8362.



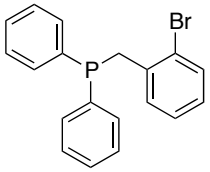
Bis[tris(2-bromobenzyl)phosphine] gold chloride (11):[53] A dry tube containing the chloro(tetrahydrothiophene) gold (100 mg, 0.30 mmol) was transferred into the glove box and dissolved in dry CH_2Cl_2 (0.5 mL). To the tube was added tris(2-bromobenzyl)phosphine (**3**) (340 mg, 0.60 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 30 min the tube was taken out of the glove box and the solution was concentrated by rotary evaporation. The product precipitated as a practically insoluble white powder in 70% yield (276 mg, 0.20 mmol). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.47 (d, *J* = 8.3 Hz, 1H), 7.42 (d, *J* = 7.1 Hz, 1H), 7.16 (t, *J* = 7.1 Hz, 1H), 7.01 (*b*s, 1H), 3.97 (*b*s, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 133.7 (CH), 133.3 (CH), 129.8 (CH), 128.6 (CH), 125.2 (C), 33.3 (CH_2). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 45.94 (*b*s). HRMS-ESI: *m/z* calcd for $C_{42}H_{36}AuBr_6P_2$: 1274.7032; found 1274.6977.



[Tris(2-bromobenzyl)phosphine] gold trichloride (14): Chloro[tris(2-bromobenzyl)phosphine] gold (**7**) (16.0 mg, 0.02 mmol) was dissolved in CH_2Cl_2 (0.5 mL) in the glove box. (Dichloroiodo)benzene[54] (7.0 mg, 0.025 mmol) was added in CH_2Cl_2 (0.5 mL) and the solution was stirred for 6 h in the absence of light. The flask was removed from the glove box and the solution was concentrated by rotary evaporation. The highly concentrated solution was then layered with pentane and over the day orange crystals suitable for X-ray diffraction

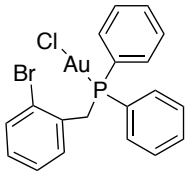
[54] Zhao, X.-F.; Zhang, C. *Synthesis* **2007**, 551-557

analysis were grown. 30% yield (5.0 mg, 0.006 mmol). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.41 (dt, *J* = 7.7, 1.8 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.25-7.23 (m, 1H), 4.15 (d, *J* = 12.7 Hz, 2H).^{13}C NMR (126 MHz, CD_2Cl_2) δ 134.4 (CH), 134.3 (CH), 129.9 (CH), 129.9 (C), 126.0 (CH), 125.9 (C), 31.5 (d, *J* = 32.2 Hz, CH2). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 51.99 (s).



(2-Bromobenzyl)diphenylphosphine (4): To a solution of diphenylphosphine chloride (0.8 mL, 4.5 mmol) in dry THF (15 mL) was added 2-bromobenzyl magnesium bromide (27 mL, 6.80 mmol, 0.25 M in THF) at 0ºC. When at room temperature the ice-bath was removed and the solution was left stirring until all chlorophosphine had been consumed (^{31}P NMR). The solution was then cooled down to 0ºC and BH_3·THF complex (15 mL, 15 mmol, 1M in THF) was added. The solution was left stirring until reaching room temperature and all phosphine had been protected (^{31}P-NMR), normally 2h. The reaction was carefully quenched by the slow addition of H_2O at 0ºC. The two organic phases were separated and the aqueous phase washed once with EtOAc. The organic fractions were combined, dried and concentrated onto Florisil. The concentrated product was then purified by column chromatography (3% EtOAc in cyclohexane) and the purified protected phosphine was transferred into a dried flask. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.67-7.62 (m, 4H), 7.55-7.51 (m, 2H), 7.47-7.42 (m, 5H), 7.23-7.16 (m, 2H), 7.10-7.06 (m, 1H), 3.89 (d, *J* = 12.0 Hz, 2H). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 21.73 (d, J = 64.4). ^{11}B NMR (160 MHz, CD_2Cl_2) δ -38.68 (d, J = 54.7 Hz). Degassed $NHEt_2$ was added and the solution was stirred for 3h at 50ºC or until all phosphine had been deprotected (^{31}P NMR). The excess amine was removed by inert evaporation and the resulting oil was dissolved in dry degassed CH_2Cl_2 and filtered inertly over a plug of celite into a tarred flask. The solvent was

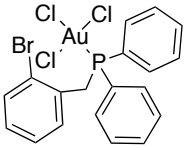
concentrated under the hood and the resulting oil was transferred into the glove box. Phosphine (**4**) was isolated as a sticky oil in 38% yield (620 mg, 1.75 mmol (including 10% of the oxidized phosphine)). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.54-7.53 (m, 1H), 7.45-7.41 (m, 5H), 7.35-7.34 (m, 5H), 7.07-7.01 (m, 2H), 6.84 (dt, J = 7.3 Hz, 1.9 Hz, 1H) 3.58 (s, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) *δ* 137.9 (C), 137.2 (C), 132.9 (CH), 132.8 (CH), 132.7 (CH), 130.9 (CH), 128.7 (CH), 128.3 (CH), 128.3 (CH), 127.5 (CH), 126.9 (CH), 99.9 (C), 36.1 (CH_2). ^{31}P NMR (162 MHz, CD_2Cl_2) *d* -9.83 (s), 31.09 (s). HRMS-ESI: *m/z* calcd for $C_{19}H_{17}BrP$: 355.0246; found 355.0256. The spectral data is in accordance with previously reported synthesis[55].



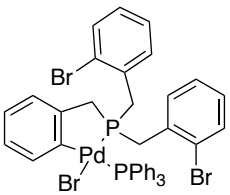
Chloro[(2-bromobenzyl)diphenylphosphine] gold (8):[53] A dry tube containing the chloro(tetrahydrothiophene) gold (20.0 mg, 0.06 mmol) was transferred into the glove box and dissolved in dry CH_2Cl_2 (0.5 mL). To the tube was added (2-bromobenzyl)diphenylphosphine (**4**) (26.0 mg, 0.075 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 30 min the tube was taken out of the glove box and the solution was concentrated. The residue was then redissolved in CH_2Cl_2 and passed through a pipette filled with silica. The solution was concentrated, resulting in the pure complex as a white solid in 64% yield (22.6 mg, 0,038 mmol). Crystals suitable for x-ray diffraction analysis were grown from a saturated dichloromethane solution layered with pentane. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.71-7.67 (m, 4H), 7.59-7.56 (m, 3H), 7.52-7.49 (m, 4H), 7.17-7.11 (m, 2H), 6.94-6.91 (m, 1H), 4.05 (d, *J* = 12.3 Hz, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 135.6 (CH), 135.5 (CH), 135.2 (CH), 134.1 (C), 134.1 (CH), 133.6 (CH), 131.2 (CH), 131.1 (CH), 131.0 (CH),

[55] Morales-Morales, D.; Redón, R.; Zheng, Y.; Dilwort, J. R. *Inorg. Chim. Acta* **2002**, 39-44.

130.8 (C), 130.3 (C), 129.5 (CH), 37.6 (d, *J* = 36.1, CH2). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 34.00 (s). HRMS-ESI: *m/z* calcd for $C_{19}H_{16}AuClBrPNa$: 608.9419; found 608.9409.



[(2-Bromobenzyl)diphenylphosphine] gold trichloride (15): Chloro[(2-bromobenzyl)diphenylphosphine] gold (**8**) (66 mg, 0.11 mmol, 1 eq) was dissolved in CH_2Cl_2 (5 mL). (Dichloroiodo)benzene[56] (37 mg, 0.13 mmol) was added in CH_2Cl_2 (5 mL) and the solution was stirred for 6 h in absence of light. The solvent was concentrated and the highly concentrated solution was then layered with pentane and over the day crystals suitable for X-ray diffraction analysis were grown. 55% yield (40 mg, 0.061 mmol). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.70-7.68 (m, 2H), 7.60-7.48 (m, 9H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.27 (t, J = 7.1 Hz, 1H), 7.15 (tt, J = 7.3 Hz, 1H), 4.77 (d, *J* = 13.8 Hz, 2H).^{13}C NMR (126 MHz, CD_2Cl_2) δ 136.3, 136.1, 135.4, 133.6, 132.2, 131.3, 131.2, 130.3, 123.5, 122.9, 34.8. ^{31}P NMR (162 MHz, CD_2Cl_2) δ 51.99 (s).

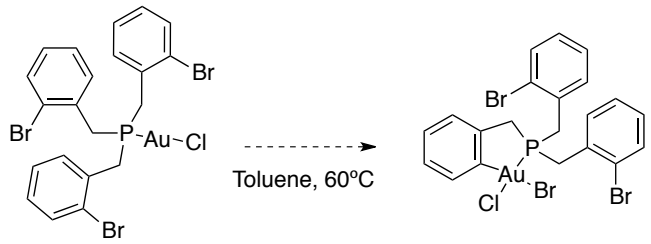


Palladium(II) -triphenylphosphine-(tris(2-bromobenzyl)phosphine) (16): Tris(2-bromobenzyl)phosphine (47 mg, 0.09 mmol) (**3**) was mixed with palladium(0)tetrakis triphenylphosphine (100 mg, 0.09 mmol) in toluene in the glove box over night. The solvent was evaporated and the palladacycle was purified by preparative TLC in 12% yield (10 mg, 0.01 mmol). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.81 (d, *J* = 6.1 Hz, 2H), 7.63 (t, *J* = 8.9 Hz, 6H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.44 – 7.41 (m, 2H), 7.36 (t, *J* = 7.5 Hz, 9H), 7.17 (t, *J* = 7.1 Hz, 2H), 7.04 (t, *J* = 7.6

[56] Zhao, X.-F.; Zhang, C. *Synthesis* **2007**, 551-557

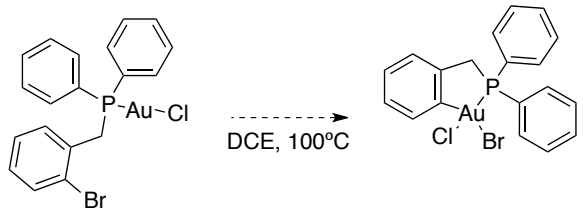
Hz, 2H), 6.93 (d, *J* = 6.5 Hz, 1H), 6.60 (t, *J* = 7.7 Hz, 1H), 6.43 (m, 1H), 6.11 (t, *J* = 7.4 Hz, 1H), 3.99 (dd, *J* = 14.0, 9.4 Hz, 2H), 3.75 (td, *J* = 13.7, 5.1 Hz, 2H), 3.30 (dd, *J* = 10.9, 1.7 Hz, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 147.3 (s, C), 140.2 (s, CH), 135.5 (s, CH), 134.6 (s, C), 133.2 (s, CH), 132.6 (s, CH) 130.6 (s, CH), 128.9 (s, CH), 128.5 (s, CH), 127.8 (s, CH), 125.2 (s, C), 124.7 (s, CH) 124.5 (s, CH), 124.5 (s, CH), 124.3 (s, CH), 38.4 (s, CH_2), 33.0 (s, CH_2). ^{31}P NMR (202 MHz, CD_2Cl_2) δ 61.80 (dt, *J* = 413.8, 10.9 Hz), 26.38 (d, *J* = 413.8 Hz). HRMS-ESI: *m/z* calcd for $C_{39}H_{33}Br_3P_2Pd$: 824.9465; found 824.9471.

Attempted Synthesis of Gold (III) Complex (4').



Chloro[tris(2-bromobenzyl)phosphine] gold complex **7** was dissolved in dry toluene and stirred over night at RT in the glove box. After monitoring the reaction by NMR (^{31}P) the tube was removed from the glove box and stirred under an argon atmosphere in the fume hood at 60ºC. The reaction was monitored for several days without the detection of formation of either auracycle or decomposed Au(0).

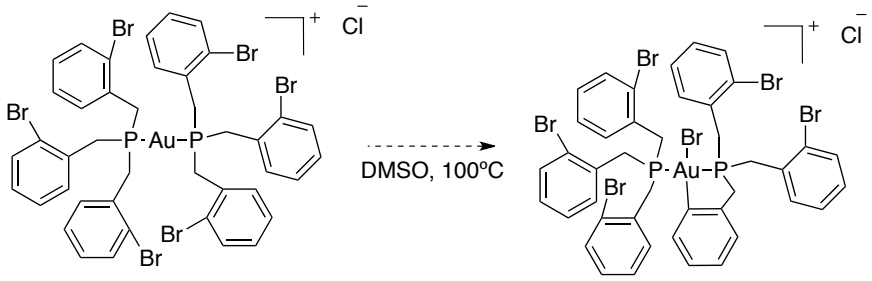
Attempted Synthesis of Gold (III) Complex (8').



Chloro[(2-bromobenzyl)diphenylphosphine] gold complex **8** was dissolved in DCE and stirred over night in the fume hood at 100ºC. The reaction was

monitored for several days without the detection of formation of either auracycle or decomposed Au(0).

Attempted Synthesis of Gold (III) Complex (11').



Cationic bis[tris(2-bromobenzyl)phosphine] gold chloride complex **11** was dissolved in DMSO and stirred at 100ºC for several days without the detection of formation of either auracycle or decomposed Au(0).

Computational details

All reported calculations were performed by the means of the Gaussian 09 suite of programs. Density Functional Theory (DFT) has been employed using the Meta-Hybrid Generalised Gradient Approximation (MH-GGA) M06 functional. The SDD basis set and ECP was used to describe Au, Pd and I atoms, while 6-31+G(d) was used for all remaining atoms. Optimisations are performed in water, through an implicit solvent PCM model. Stationary points are tested by the calculation of frequencies. Additionally, Intrisic Reaction Coordinate (IRC) calculations confirmed connection on the PES between reactants, transition states and products.

Crystal structures

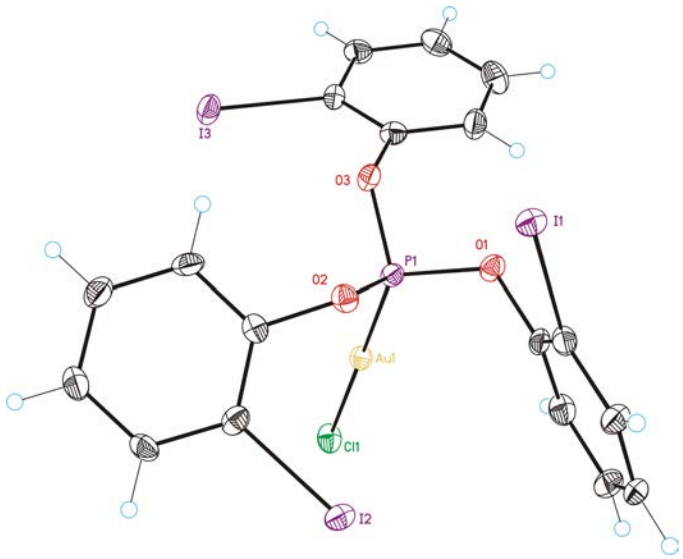


Figure 1. Crystal structure of complex 2a. Carbon atoms are shown in light gray, hydrogen atoms in white, oxygen atoms in red, gold atom in yellow, phosphorous and iodine atoms in purple and chloride in green.

Table 1. Crystal data and structure refinement for complex 2a.

Identification code	complex 2a
Empirical formula	C18 H12 Au Cl I3 O3 P
Formula weight	920.36
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 11.0595(5) Å
	⟨= 90.00 °.
	b = 12.7552(6) Å

	® = 105.0190(10) °.
	c = 16.4234(8) Å
	© = 90.00 °.
Volume	2237.64(18) Å^3
Z	4
Density (calculated)	2.732 Mg/m^3
Absorption coefficient	10.920 mm^{-1}
F(000)	1656
Crystal size	0.25 x 0.10 x 0.03 mm^3
Theta range for data collection	2.00 to 30.03 °.
Index ranges	-14 <=h<=15 ,-17 <=k<=15 ,-22
<=l<=21	
Reflections collected	5473
Independent reflections	4935 [R(int) = 0.0401]
Completeness to theta =30.03 °	0.837 %
Absorption correction	Empirical
Max. and min. transmission	0.98 and 0.81
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5473 / 0 / 244
Goodness-of-fit on F^2	0.761
Final R indices [I>2sigma(I)]	R1 = 0.0268 , wR2 = 0.0859
R indices (all data)	R1 = 0.0307 , wR2 = 0.0918
Largest diff. peak and hole	1.739 and -1.597 e.Å^{-3}

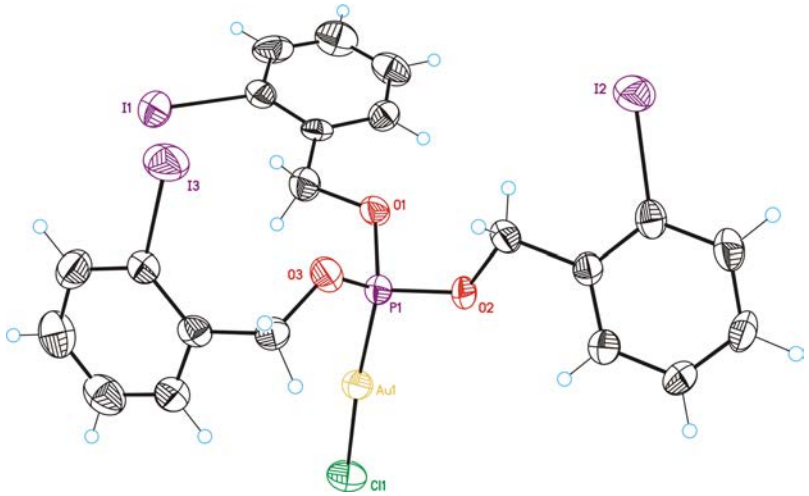


Figure 2. Crystal structure of complex 2b. Carbon atoms are shown in light gray, hydrogen atoms in white, oxygen atoms in red, gold atom in yellow, phosphorous and iodine atoms in purple and chloride in green.

Table 2. Crystal data and structure refinement for complex 2b.

Identification code	complex 2b
Empirical formula	C21 H18 Au Cl I3 O3 P
Formula weight	962.44
Temperature	300(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	a = 18.718(2) Å〈= 90°.
	b = 8.0042(12) Å®= 90°.

	c = 33.333(5) Å© = 90°.
Volume	4994.0(13) $Å^3$
Z	8
Density (calculated)	2.560 Mg/m^3
Absorption coefficient	9.792 mm^{-1}
F(000)	3504
Crystal size	0.21 x 0.20 x 0.20 mm^3
Theta range for data collection	1.22 to 25.04°.
Index ranges	-22<=h<=19, -8<=k<=9, -
39<=l<=38	
Reflections collected	29265
Independent reflections	4402 [R(int) = 0.0705]
Completeness to theta = 25.04°	99.5 %
Max. and min. transmission	0.2448 and 0.2329
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4402 / 0 / 271
Goodness-of-fit on F^2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0340, wR2 = 0.0634
R indices (all data)	R1 = 0.0491, wR2 = 0.0727
Largest diff. peak and hole	0.757 and -0.904 $e.Å^{-3}$

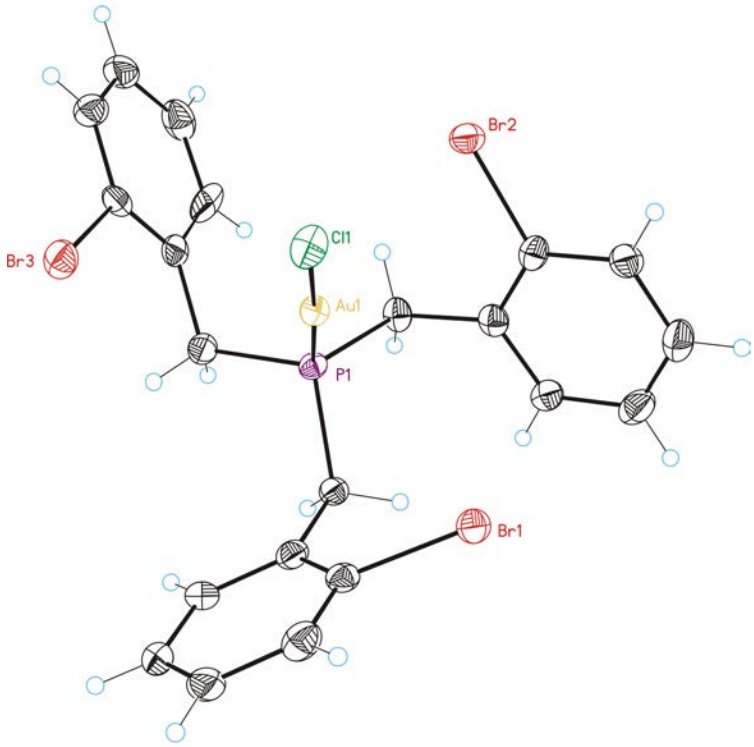


Figure 3. Crystal structure of complex 4. Carbon atoms are shown in light gray, hydrogen atoms in white, gold atom in yellow, phosphorous atoms in purple, bromide atoms in red and chloride atom in green.

Table 3. Crystal data and structure refinement for complex 4.

Identification code	complex 4
Empirical formula	C23 H21 Au Br3 Cl N P
Formula weight	814.52
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 12.6165(5) Å
	⟨= 90.00 °.

	b = 13.1976(4) Å
	® = 90.00 °.
	c = 14.9182(5) Å
	© = 90.00 °.
Volume	2483.99(15) Å^3
Z	4
Density (calculated)	2.178 Mg/m^3
Absorption coefficient	10.932 mm^{-1}
F(000)	1528
Crystal size	0.20 x 0.20 x 0.15 mm^3
Theta range for data collection	2.06 to 30.03 °.
Index ranges	-16 <=h<=16 ,-18 <=k<=17 ,-19
<=l<=19	
Reflections collected	17891
Independent reflections	6257 [R(int) = 0.0445]
Completeness to theta =30.03 °	0.898 %
Absorption correction	Empirical
Max. and min. transmission	0.1983 and 0.1113
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6257 / 6 / 272
Goodness-of-fit on F^2	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0326 , wR2 = 0.0807
R indices (all data)	R1 = 0.0339 , wR2 = 0.0814
Absolute Structure Flack parameter	x =-0.0008(7)
Largest diff. peak and hole	3.287 and -1.474 e.Å^{-3}

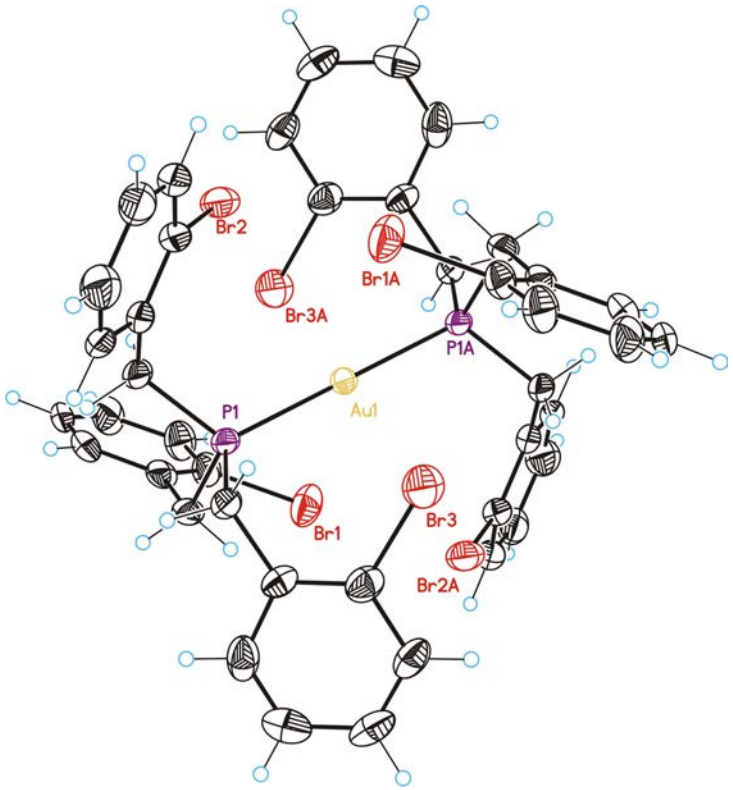


Figure 4. Crystal structure of complex 5. Carbon atoms are shown in light gray, hydrogen atoms in white, gold atom in yellow, phosphorous atoms in purple, bromide atoms in red and chloride atom in green.

Table 4. Crystal data and structure refinement for complex 5.

Identification code	complex 5
Empirical formula	C46.50 H44 Au Br6 Cl8.50 P2
Formula weight	1642.51
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 17.0229(14) Å

	⟨= 90.00 °.
	b = 16.1927(14) Å
	® = 106.408(3) °.
	c = 20.3819(17) Å
	© = 90.00 °.
Volume	5389.4(8) Å^3
Z	4
Density (calculated)	2.024 Mg/m^3
Absorption coefficient	7.693 mm^{-1}
F(000)	3146
Crystal size	0.30 x 0.10 x 0.10 mm^3
Theta range for data collection	1.77 to 30.04 °.
Index ranges	-22 <=h<=23 ,-22 <=k<=22 ,-28 <=l<=28
Reflections collected	51011
Independent reflections	7285 [R(int) = 0.0381]
Completeness to theta =30.04 °	0.923 %
Absorption correction	Empirical
Max. and min. transmission	0.5134 and 0.2062
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7285 / 112 / 322
Goodness-of-fit on F^2	1.083
Final R indices [I>2sigma(I)]	R1 = 0.0443 , wR2 = 0.1121
R indices (all data)	R1 = 0.0621 , wR2 = 0.1229
Largest diff. peak and hole	1.736 and -1.391 e.Å^{-3}

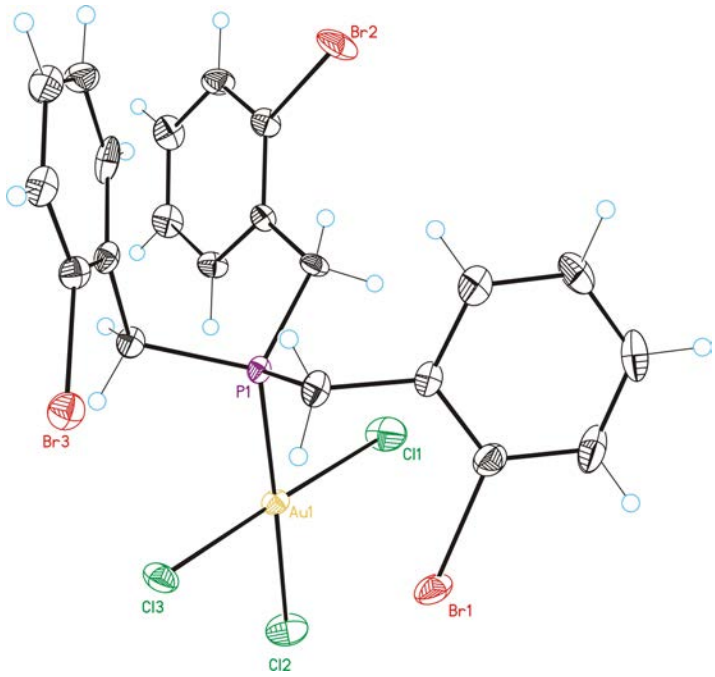


Figure 5. Crystal structure of complex 4b. Carbon atoms are shown in light gray, hydrogen atoms in white, gold atom in yellow, phosphorous atoms in purple, bromide atoms in red and chloride atom in green.

Table 5. Crystal data and structure refinement for complex 4b.

Identification code	complex 4b
Empirical formula	C21 H18 Au Br3 Cl3 P
Formula weight	844.37
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.7999(9) Å
	⟨= 110.522(2) °.

	b = 10.9675(9) Å
	® = 94.248(2) °.
	c = 11.0350(9) Å
	© = 99.807(3) °.
Volume	1193.49(17) Å^3
Z	2
Density (calculated)	2.350 Mg/m^3
Absorption coefficient	11.596 mm^{-1}
F(000)	788
Crystal size	0.25 x 0.15 x 0.10 mm^3
Theta range for data collection	1.93 to 29.89 °.
Index ranges	-15 <=h<=14 ,-15 <=k<=14 ,-14
<=l<=14	
Reflections collected	19268
Independent reflections	6062 [R(int) = 0.0558]
Completeness to theta =29.89 °	0.878 %
Absorption correction	Empirical
Max. and min. transmission	0.3204 and 0.1446
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6062 / 0 / 271
Goodness-of-fit on F^2	1.059
Final R indices [I>2sigma(I)]	R1 = 0.0520 , wR2 = 0.1458
R indices (all data)	R1 = 0.0591 , wR2 = 0.1519
Largest diff. peak and hole	4.485 and -5.346 e.Å^{-3}

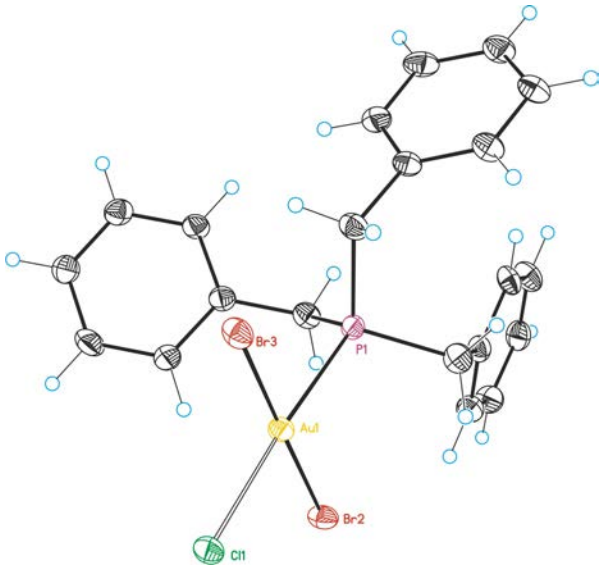


Figure 6. Crystal structure of complex 4c. Carbon atoms are shown in light gray, hydrogen atoms in white, gold atom in yellow, phosphorous atoms in purple, bromide atoms in red and chloride atom in green.

Table 6. Crystal data and structure refinement for complex 4c.

Identification code	complex 4c
Empirical formula	C26 H31 Au Br2 Cl1.40 P
Formula weight	780.89
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	a = 11.3849(14) Å
	b = 19.084(2) Å
	c = 23.787(3) Å
Volume	5168.2(11) $Å^3$
Z	8

Density (calculated)	2.007 Mg/m^3
Absorption coefficient	9.005 mm^{-1}
F(000)	2998
Crystal size	0.10 x 0.10 x 0.10 mm^3
Theta range for data collection	2.25 to 36.20 °.
Index ranges	-17 <=h<=10 ,-26 <=k<=31 ,-31 <=l<=38
Reflections collected	39404
Independent reflections	11934 [R(int) = 0.0584]
Completeness to theta =36.20 °	0.962 %
Absorption correction	Empirical
Max. and min. transmission	0.4662 and 0.4662
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11934 / 155 / 325
Goodness-of-fit on F^2	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0482 , wR2 = 0.1060
R indices (all data)	R1 = 0.0976 , wR2 = 0.133
Largest diff. peak and hole	3.843 and -5.032 $e.Å^{-3}$

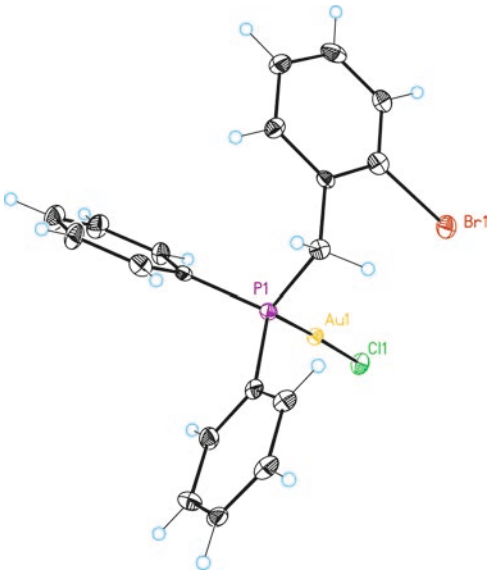


Figure 7. Crystal structure of complex **8**. Carbon atoms are shown in light gray, hydrogen atoms in white, gold atom in yellow, phosphorous atoms in purple, bromide atoms in red and chloride atom in green.

Table 7. Crystal data and structure refinement for mo_MLd84_0m.

Identification code		mo_MLd84_0m
Empirical formula		C19 H16 Au Br Cl P
Formula weight		587.61
Temperature		100(2)K
Wavelength		0.71073 Å
Crystal system		Monoclinic
Space group		P2(1)/n
Unit cell dimensions	a = 8.4286(9) Å	a= 90.00 °.
	b = 16.0606(18) Å	b = 106.295(4) °.
	c = 13.9197(16) Å	g = 90.00 °.
Volume		1808.6(3) Å^3
Z		4
Density (calculated)		2.158 Mg/m^3

Absorption coefficient	10.575 mm^{-1}
F(000)	1104
Crystal size	0.30 x 0.18 x 0.10 mm^3
Theta range for data collection	1.98 to 30.24 °.
Index ranges	-11 <=h<=9 ,-22 <=k<=21 ,-13 <=l<=19
Reflections collected	15740
Independent reflections	4852 [R(int) = 0.0595]
Completeness to theta =30.24 °	0.901 %
Absorption correction	Empirical
Max. and min. transmission	0.4177 and 0.1436
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4852 / 0 / 208
Goodness-of-fit on F^2	1.052
Final R indices [I>2sigma(I)]	R1 = 0.0404 , wR2 = 0.1082
R indices (all data)	R1 = 0.0525 , wR2 = 0.1185
Largest diff. peak and hole	3.678 and -3.188 e.$Å^{-3}$

UNIVERSITAT ROVIRA I VIRGILI
MECHANISTIC STUDIES ON GOLD MEDIATED CROSS-COUPLING REACTIONS AND TOTAL SYNTHESIS OF (_+)-EPIGLOBULOL
Madeleine Livendahl
Dipòsit Legal: T.1507-2013

Total Synthesis of Agrimonol, an open door to the total synthesis of Cladosporin and its analogues

Introduction

The need of a new antimalarial treatment is of great importance. *Plasmodium falciparum* is a protozoan parasite that causes the most dangerous form of malaria. It has the highest rate of complications and mortality. Almost all malarial deaths are caused by *p. falciparum*. An increasing resistance of *p. falciparum* to several well known antimalarial drugs makes it highly desirable for a new antimalarial treatment especially directed to inhibit the blood and liver stage proliferation of this parasite. Malaria is a global disease but is most burdened in the sub-Saharan regions of Africa.[1] The falciparum malaria there affects mostly small children and pregnant women. Due to the poverty of these regions, the mostly used antimalarial treatments are based on old drugs such as chloroquine, sulfadoxine/pyrimethamine, quinine and amodiaquine. Often purchased in sub-therapeutic doses and subsequently treatment in the home, due to inability to travel to local clinics. This in turns leads to low drug concentrations lingering in the blood, which is a powerful selective pressure for the development of resistant parasites. Artemisinin, which is active against *p. falciparum* is recommended by the World Health Organization (WHO) to be administered only in the combination with another antimalarial drug. It was discovered in 1972 by researchers investigating the active ingredient in a Chinese medicinal plant *Artemisia annua*.[2] It has an interesting structure bearing an endoperoxide moiety (figure 3. 1).

[1] Snow, R. W.; Guerra, C. A.; Noor, A. M.; Myint, H. Y.; Hay, S. I. *Nature* **2005**, *434*, 214-217.
[2] Miller, L. H.; Su, X. *Cell* **2011**, *6*, 855-858.

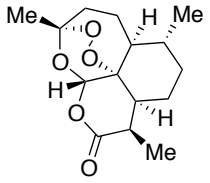
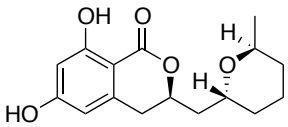


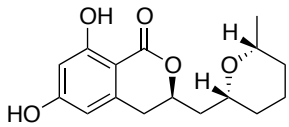
Figure 3. 1. Artemisinin

One drawback of the treatment is its short half-life in the body. This has led to "recrudescence" which effectively means that a small number of malaria parasites survive the treatment and continue to multiply.[3] Derivatives of Artemisinin have been synthesized to reduce the problem of recrudescence as well as to improve the formulation properties of the non-polar molecule of Artemisinin. Researchers from Berkeley recently reported the complete biosynthetic pathway towards Artemisinin.[4] The method has potential to give a low costing access for developing countries to these types of first-line anti-malarial drugs.

This class of endoperoxide drugs have one major drawback; their lack of activity against the asymptomatic malaria liver stages. Next generation antimalarials would need to be active against multidrug-resistance as well as be efficacious against liver- and blood-stage infections.



Cladosporin



Isocladosporin

[3] (a) Nosten, F.; White, N. J. *Am. J. Trop. Med. Hyg.* **2007**, *77*, 181-192. (b) Codd, A.; Teuscher, F.; Kyle, D. E.; Cheng, Q.; Gatton, M. L. *Malaria Journal* **2011**, 10:56

[4] Paddon, C. J.; Westfall, P. J.; Pitera, D. J.; Benjamin, K.; Fisher, K.; McPhee, D.; Leavell, M. D.; Tai, A.; Main. A.; Eng, D.; Polichuk, D. R.; Teoh, K. H.; Reed, D. W.; Treynor, T.; Lenihan, J.; Fleck, M.; Bajad, S.; Dang, G.; Diola, D.; Dorin, G.; Ellens, K. W., Fickes, S.; Galazzo, J.; Gaucher, S. P.; Geistlinger, T.; Henry, R.; Hepp, M.; Horning, T.; Iqbal, T.; Jiang, H.; Kizer, L.; Lieu, B.; Melis, D.; Moss, N.; Regentin, R.; Secrest, S.; Tsuruta, H.; Vazquez, R.; westblade, L. F.; Xu, L.; Yu, M.; Zhang, Y.; Zhao, L.; Lievense, J.; Covello, P. S.; Keasling, J. D.; Reiling, K. K., Renninger, N. S.; Newman, J. D. *Nature* **2013**, doi: 10.1038/nature12051

Cladosporin an antifungal antibiotic and plant growth inhibitory metabolite[5] produced by various fungal sources such as *cladosporium cladosporioides* and *aspergillus flavus* was characterized fully by Vederas et al.[6] In 2012 Hoepfner and Winzeler *et. al.*[7] demonstrated that Cladosporin exhibits a striking selective activity against *p. falciparum* blood and liver stage proliferation (in the nanomolar range). It was shown to specifically inhibit protein synthesis by directly targeting *p. falciparum* cytosolic lysyl t-RNA synthetase. They conclude that lysyl-tRNA synthetase is an attractive, druggable, antimalarial target that can be selectively inhibited. Despite its high selectivity and strong potency, Cladosporin exhibit a poor metabolic stability. Due to this low oral bioavailability a convergent synthetic route had to be designed in order to access not only the parent compound, but also to its analogues.

[5] Jacnyo, J. M.; Harwood, J. S.; Cutler, H. G.; Lee, M.-K. *J. Nat. Prod.* **1993**, *56*, 1397-1401.

[6] Reese, P. B.; Rawlings, B. J.; Ramer, S. E.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 316-318.

[7] Hoepfner, D.; McNamara, C. W.; Lim, C. S.; Studer, C.; Riedl, R.; Aust, T.; McCormack, S. L.; Plouffe, D. M.; Meister, S.; Schuierer, S.; Plikat, U.; Hartmann, N.; Staedler, F.; Cotesta, S; Schmitt, E. K.; Petersen, F.; Supek, F.; Glynne, R. J.; Tallarico, J. A.; Porter, J. A; Fishman, M. C.; Bodenreider, C.; Diagana, T. T.; Movva, R. N.; Winzeler, E. A. *Cell Host & Microbe* **2012**, *11*, 654-663.

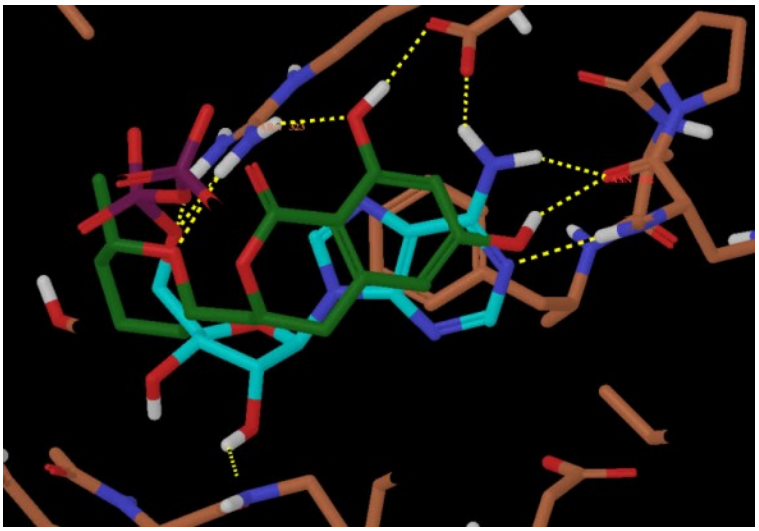
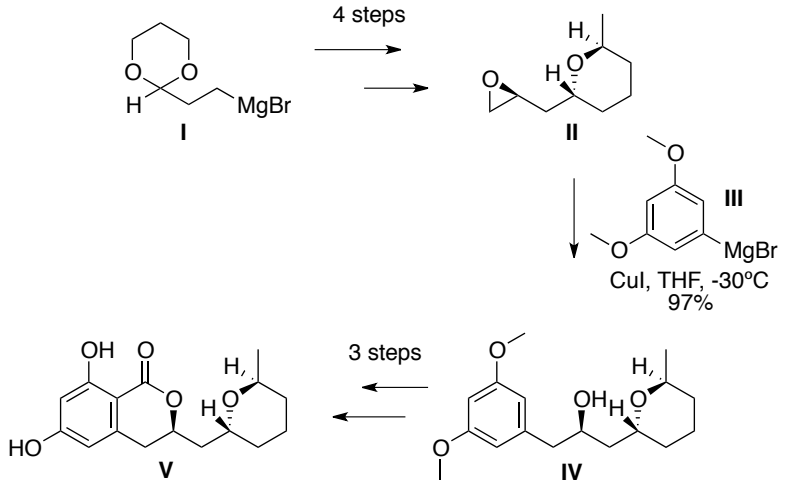


Figure 3. 2. In silico docking of Cladosporin in ATP binding site.

While we were embarking on the total synthesis of Cladosporin and searching for the most flexible route, two reports were published. The first results were published by the group of She[8] in 2012. The key step of the synthesis relies on the formation of the Gilman copper reagent of the aryl Grignard (**III**) resulting into the selective attack on to the epoxide (**II**) derived from allyl pyran (scheme 3. 1). The high yielding coupling was performed in the presence of CuI in THF at -30ºC. The so-formed alcohol intermediate was then reacted with trimethyl ortho formate in an oxa-Pictet Spengler reaction. Following an oxidation and deprotection sequence of the methyl ethers the authors could access (-)-Cladosporin in a total of 8 steps and 8% overall yield.

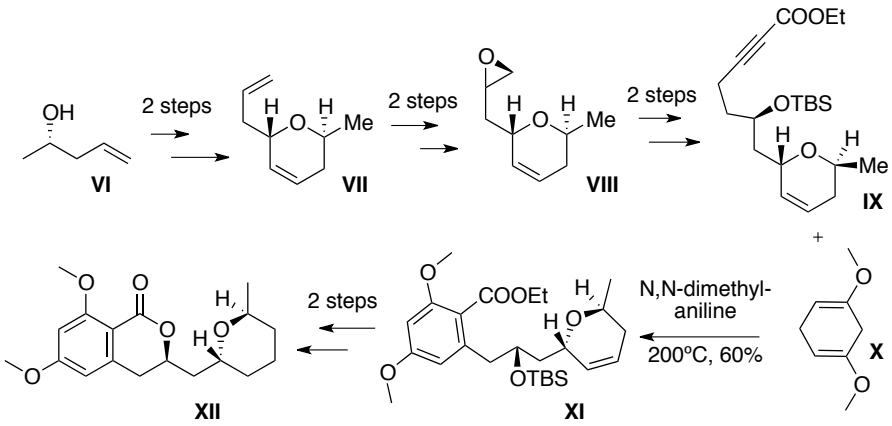
[8] Zheng, H.; Zhao, C.; Fang, B.; Jing, P.; Yang, J.; Xie, X.; She, X. *J. Org. Chem.* **2012**, *77*, 5656-5663.



Scheme 3. 1. Key step of the total synthesis of Cladosporin

The second reported synthesis of Cladosporin was made by the group of Mohaptra[9] in 2013. The authors installed the pyran ring moiety scaffold from commercially available allyl alcohol and coupling it to an *α-β*-unsaturated aldehyde through a cross-metathesis reaction (scheme 3. 2). This intermediate then underwent intramolecular cyclization in the presence of allyl trimethyl silane and iodine. Thus, the authors accessed the same allyl-pyran intermediate as was described by She et. al.. After performing a Sharpless dihydroxylation and elimination, the epoxy-pyran was reacted with the lithium salt of ethyl propionate in the presence of $BF_3 \cdot Et_2O$ affording the homopropargylic alcohol (**IX**). The triple bond was then reacted in the key transformation of the synthesis with reduced compound (**X**) in an Alder-Rickert cycloaddition reaction. The so-formed aromatic resorcylate ester (**XI**) underwent intramolecular cyclization to afford the iso-coumarin ring after deprotection of the silyl ether. Reduction of the internal double bond in the pyran ring then gave access to intermediate **XII**. This constituted the formal synthesis of (-)-Cladosporin.

[9] Mohaptra, D. K.; Maity, S.; Rao, T. S.; Yadav, J. S, Sridhar, B. *Eur. J. Org. Chem.* **2013**, 2859-2863.

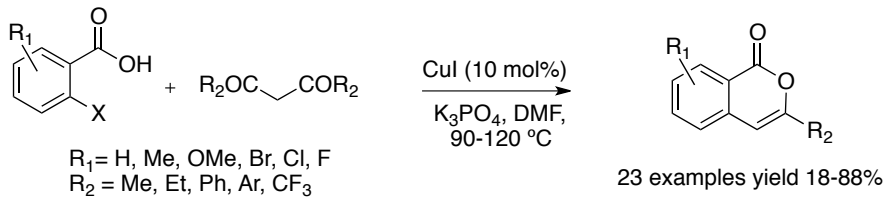


Scheme 3. 2. Formal synthesis of (-)-Cladosporin.

With the positive biological results obtained around the cladosporin scaffold we decided to design a highly versatile and simple route towards cladosporin and its analogues.

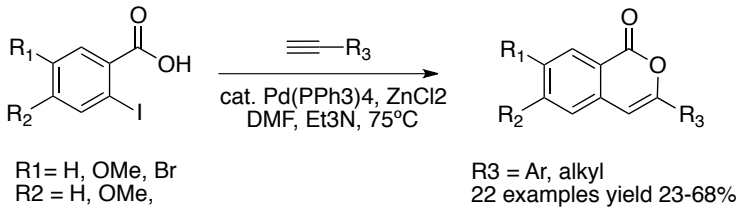
Synthesis of coumarins and *iso*-coumarin rings in organic chemistry is an important class of molecular motif especially in pharmaceutical industry due to their pharmacological properties.[10] Different groups have tackled the synthetic strategy for these kinds of scaffolds with various methods. The group of Xi[11] made a series of different *iso*-coumarin by coupling an *ortho*-halo-benzoic acid and 1,3-diketones in a copper catalyzed one-pot procedure (scheme 3. 3).

[10] (a) Matsuda, H.; Shimoda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **1999**, *7*, 1445-1450. (b) Whyte, A. C.; Gloer, J. B.; Scott, J. A.; Mallock, D. *J. Nat. Prod.* **1996**, *59*, 765-769. (c) Engelmeier, D.; Hadacek, F.; Hofer, O.; Lutz-Kutschera, G.; Nagl, M.; Wurz, G.;Greger, H. *J. Nat. Prod.* **2004**, *67*, 19-25. (d) Zhang, W.; Krohn, K.;Draeger, S.; Schulz, B. *J. Nat. Prod.* **2008**, *71*, 1078-1081.
[11] Cai, S.; Wang. F.; Xi, C. *J. Org. Chem.* **2012**, *77*, 2331-2336.



Scheme 3. 3. Copper catalyzed synthesis of iso-coumarins.

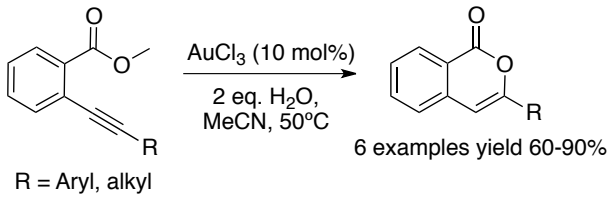
The group of Larock utilized a similar strategy by coupling *ortho*-iodo-benzoic acids with various terminal acetylenes in the presence of $Pd(PPh_3)_4$-$ZnCl_2$-Et_3N system in DMF to give direct access to iso-coumarin motifs (scheme 3. 4).



Scheme 3. 4. Synthesis of iso-coumarins.

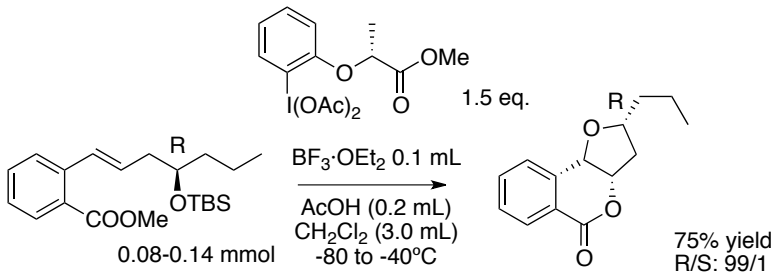
Gold catalysis has also been implemented in *iso*-coumarin and coumarin syntheses. Benzoic esters substituted with acetylenes as was used in the previous scheme makes perfect substrates for a gold mediated intramolecular cyclization reaction where gold acts as a lewis acid to activate the triple bond.[12]

[12] (a) Wegner, H. A.; Ahles, S.; Neuburger, M. *Chem. Eur. J.* **2008**, *14*, 11310-11313. (b) Marchal, E.; Uriac, P.; Legouin, B.; Toupet, L.; van de Weghe, P. *Tetrahedron* **2007**, *63*, 9979-9990. (c) Shi, Y; Roth, K. E.; Ramgren, S. D.; Blum, S. A. *J. Am. Chem. Soc.* **2009**, *131*, 18022-18023.



Scheme 3. 5. Gold catalyzed synthesis of iso-coumarins.[12b]

A stereoselective synthesis of *iso*-coumarins was reported by the group of Fujita,[13] using a chiral hypervalent iodine reagent in the presence of $BF_3 \cdot Et_2O$ (scheme 3. 6).

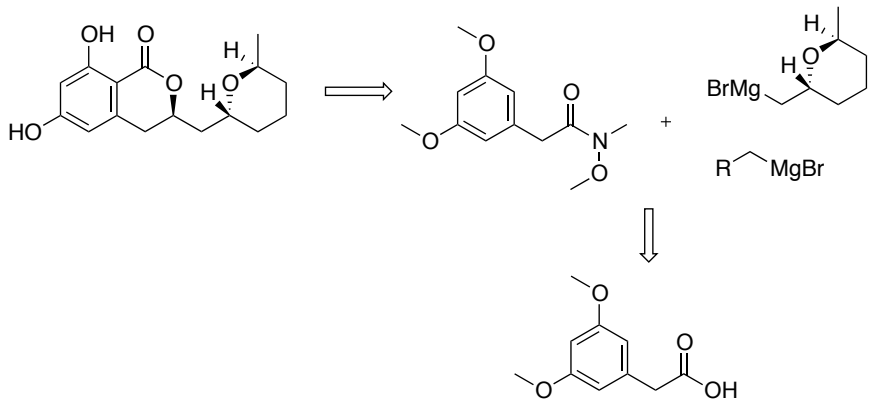


Scheme 3. 6. Asymmetric synthesis of iso-coumarins.

[13] Fujita, M.; Mori, K.; Shimogaki, M.; Sugimura, T. *Org. Lett.* **2012**, *14*, 1294-1297.

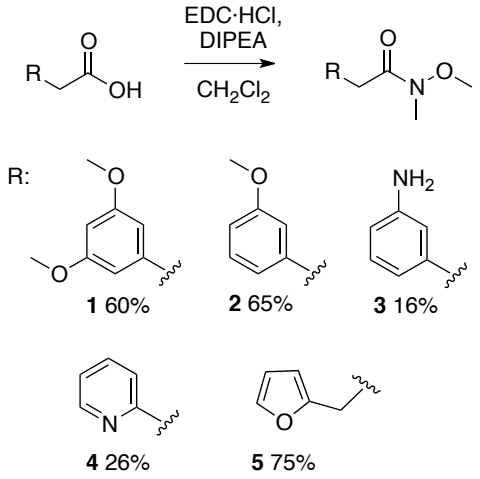
Results

Our initial retrosynthetic pathway was based on fusing both building blocks of the molecule through a nucleophilic attack from the pyran moiety or other R-(alkyl)-groups on to a Weinreb-amide bearing the aryl ring. From the generated alcohol we proposed to link together the *iso*-coumarin ring through an oxa-Pictet-Spengler reaction with trimethyl-orthoformate under acidic conditions.



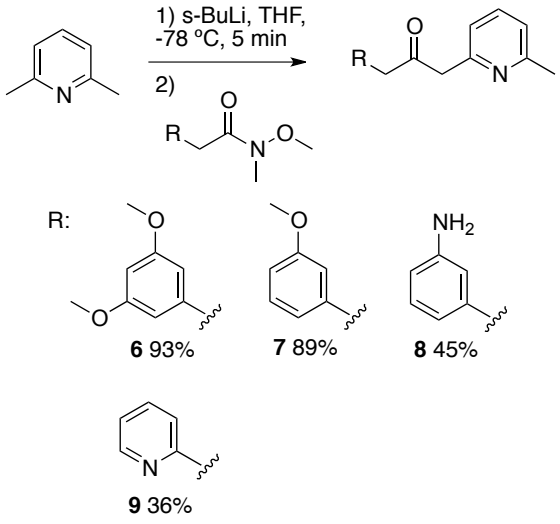
Scheme 3. 7. First retrosynthetic plan towards Cladosporin and analogues.

This methodology was designed to be the most efficient and convergent route to access a series of novel analogues bearing the *iso*-coumarin core. Weinreb amides (**1**-**5**) were all synthesized from their corresponding carboxylic acids using amide bond coupling reagent such as EDC·HCl in the presence of Hünigs base (Scheme 3. 8).



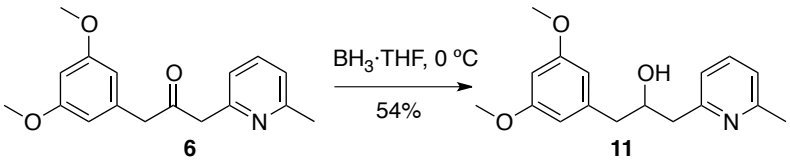
*Scheme 3. 8. Formation of Weinreb amides **1-5**.*

From the generated Weinreb amides (**1-4**) we reacted them to the lithium salt of 2,6-lutidine giving rise to the desired ketones (**6-9**).



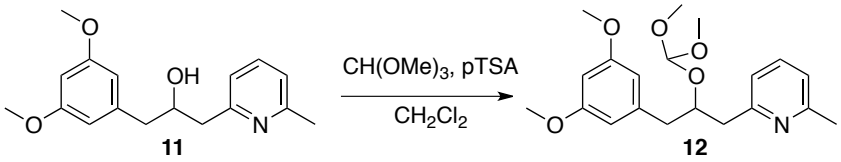
*Scheme 3. 9. Formation of ketones (**6-9**) by nucleophilic attack of 2,6-lutidine.*

Selective reduction of ketone **6** in to (R)-alcohol **10** was attempted using BH_3·THF in presence of (*S*)-Corey Bakshi Shibata (CBS)[14] known to induce high selectivity in these transformations. Unfortunately, with our substrate this reagent gave no selectivity. The racemic reduction of ketone **6** was performed in the presence of BH_3·THF (scheme 3. 10).



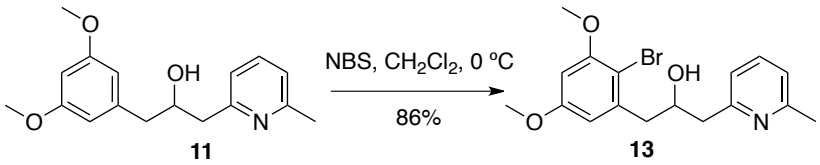
*Scheme 3. 10. Reduction of ketone **6** to racemic alcohol **11**.*

With alcohol **11** we attempted the reported oxa-Pictet-Spengler reaction using trimethyl-ortho-formate under acidic conditions (scheme 3. 11). However, with our substrate the reaction only led to intermediate (**12**).



Scheme 3. 11. Attempted oxa-Pictet-Spengler reaction.

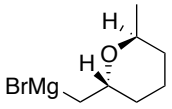
With the intention to direct the oxa-Pictet-Spengler reaction we successfully installed a bromo in the ortho-position of the aryl ring.



*Scheme 3. 12. Ortho-bromination of alcohol **11** by NBS.*

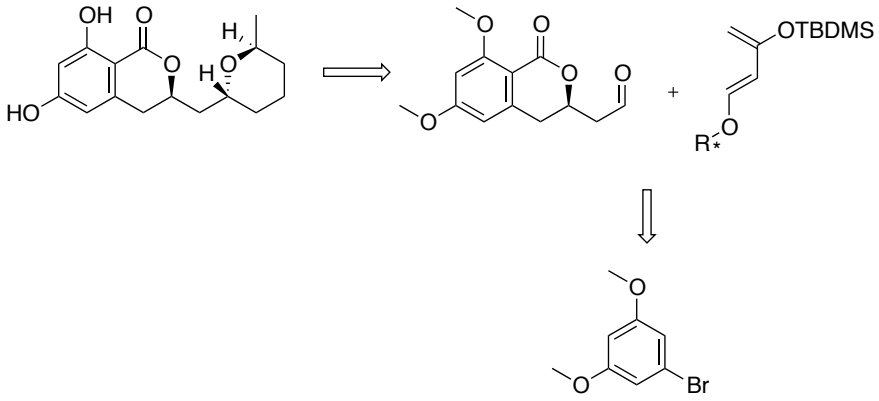
[14] Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553.

However, due to the low selectivity of the ketone reduction as well as the unsuccessful route towards Grignard reagent (**14**) developed by Dr. Marion Rusch we decided to focus on a different strategy.



14

We decided to develop another synthetic route in which we propose to build up the core molecule, taking advantage of a [4+2]hetero-diels alder reaction to form the pyran ring in a regio- and enantioselective manner.



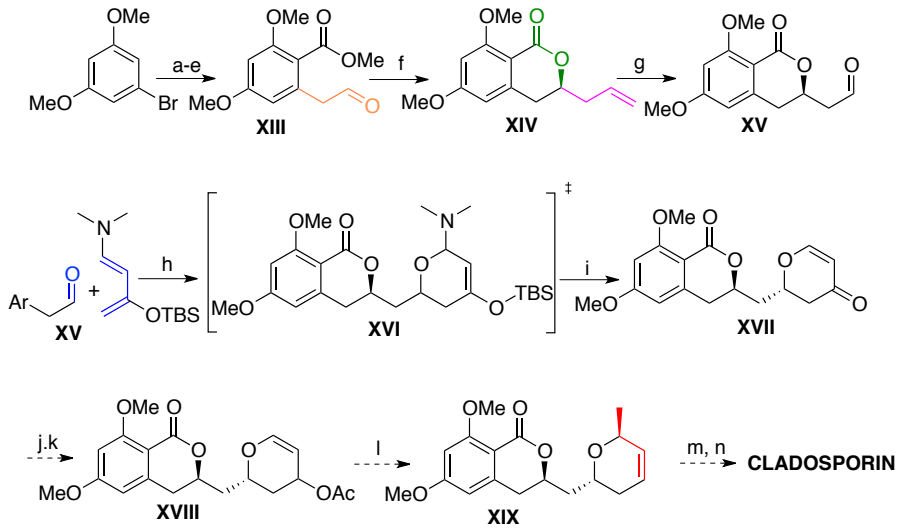
Scheme 3. 13. New retrosynthetic plan

The synthesis starts with the commercially available 3,5-dimethoxy-bromobenzene which is engaged in a Vilsmeier-Haack reaction to form the corresponding aldehyde. The aldehyde is then oxidized to the carboxylic acid using $KMnO_4$ in water. The so-formed acid undergoes an esterification in presence of K_2CO_3 and MeI. With the ester in place the bromide is exchanged for the allyl moiety through a Stille coupling. The terminal double bond undergoes oxidative cleavage by OsO_4 and $NaIO_4$ to its

corresponding aldehyde (**XIII**) followed by an enantioselective allylation in the presence of the α-pinene-allylborane reagent. Gratifyingly, the so-formed chiral allyl alcohol intermediate cyclizes intramolecularly with the internal ester to form the iso-coumarin ring (**XIV**) under mild acidic conditions. The terminal double bond of the allyl-moiety is then oxidized in the same manner as was described previously using OsO_4 and $NaIO_4$. The desired aldehyde (**XV**) is then reacted with our Danishefsky diene in a [4+2]-hetero-diels alder reaction. The pyran ring intermediate (**XVI**) is treated under acidic conditions to facilitate the removal of the chiral auxiliary and the silyl protecting group forming thus an α-β unsaturated ketone (**XVII**). The ketone is then reduced to its corresponding alcohol and further acetylated (**XVIII**). Trans-selective methylation on the double bond by trimethyl aluminium affords the double bond to rearrange and cleave the O-Acetyl group; giving the desired dihydro-pyran ring (**XIX**). This double bond is then reduced using Pd/C under one atmosphere of H_2 gas resulting in the formation of an intermediate identical to the compound previously reported in the literature.[8] Our spectroscopical data were in perfect agreement with those reported. Finally we performed the removal of the methyl ethers using a 1M solution of BBr_3 in CH_2Cl_2. This gives rise to the desired natural product (-)-Cladosporin with excellent yield and using a 13 step synthesis amenable for the production of further analogues.[15]

The key steps will involve the enantioselective boron catalyzed allylation of intermediate **XIII** and the stereoselective lanthanide catalyzed [4+2]hetero diels-alder reaction to gain access to the tricyclic core of the final product.

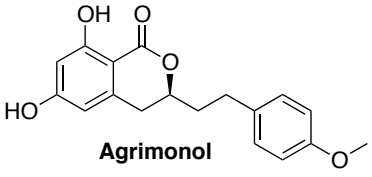
[15] Further analytical data regarding the total synthesis of Cladosporin will be reported in due course by Dr. Marion Rusch.



a) $POCl_3$, DMF, 100°C, 4h, 76%. b) $KMnO_4$, H_2O, 75°C, 4h, 64%. c) MeI, K_2CO_3, DMF, rt, 3h, 95%. d) $Pd(PPh_3)_4$, LiCl, Allyltributylstanane, DMF, 100°C, 24h, 92%. e) OsO_4, $NaIO_4$, Dioxan/water (3:1), rt, 5h, 60%. f) (+)-Ipc2BAllyl, Et2O, -78°C (1h), rt (1h), 53% yield + 7% Yield of the uncyclized allylation product. g) OsO_4, $NaIO_4$, Dioxan/water (3:1), rt, 5h, 80% h) Various conditions under investigation. i) AcCl, DCM, -78°C. j) $NaBH_4$, $CeCl_3$. 7 H_2O, MeOH, -78°C, 2h. k) Ac_2O, NEt_3, DMAP, DCM, 0°C, 2h. l) $Al(Me)_3$, DCM. m)H_2, Pd/C, MeOH, rt. n) BBr_3, DCM, rt.

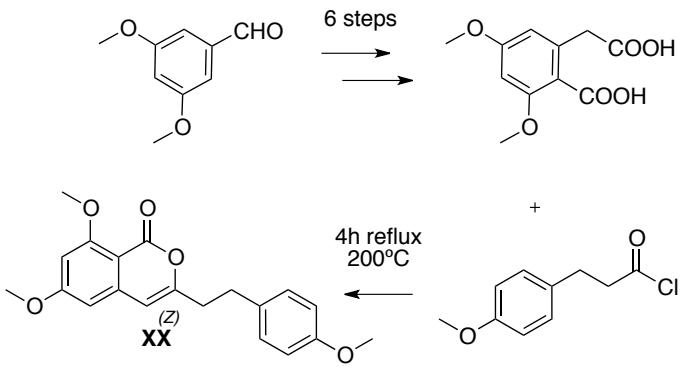
Scheme 3. 14. Total synthesis of (-)-Cladosporin.

Interestingly, an analogue of Cladosporin belonging to the iso-coumarin family was identified to be Agrimonol. The structure resembles the one of Cladosporin but bears instead of the pyran ring a methoxy substituted aryl.



With the positive results obtained around the Cladosporin scaffold we felt confident to also explore analogues like Agrimonol. So far there are only a

few reported syntheses of Agrimonol.[16] A formal non-selective synthesis of Agrimonolide was reported by the group of Badaruddin[17] which involves a 7 step synthesis towards 6,8-dimethoxy-3-[2-(4-methoxyphenyl)ethyl]-isocoumarin (**XX**) as a model for the synthesis of *DL*-agrimonolide (scheme 3. 16).

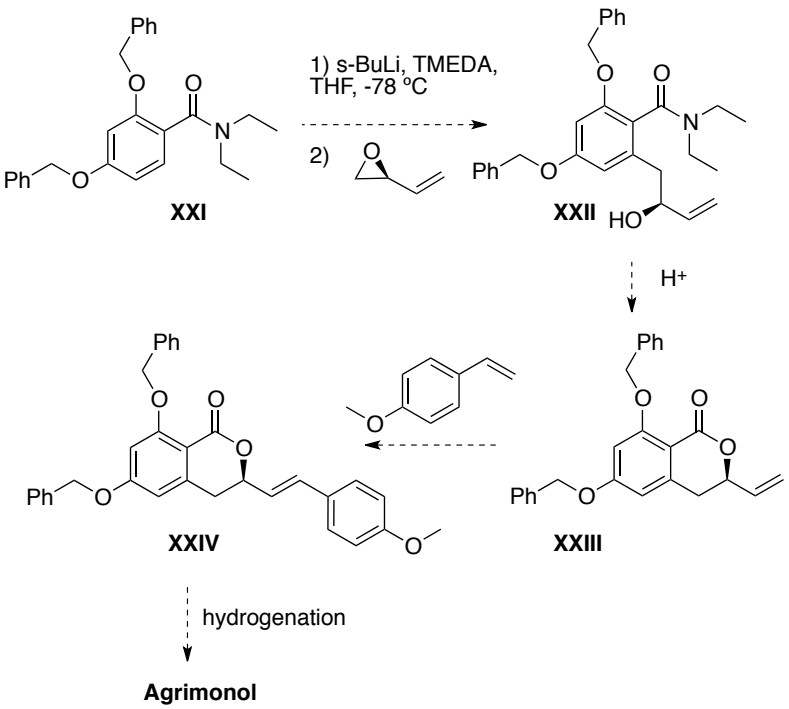


Scheme 3. 16. Synthesis of DL-agrimonolide model.

Our first synthetic route was based on the generation of a benzyl protected diethylamido intermediate **XXI** that would undergo a DOM using well known procedures developed in the laboratory of Snieckus (scheme 3. 17).[18] The expected ortho-lithiated product would then be trapped by chiral vinyl epoxide forming an alcohol, which could be cyclized on to the amine forming the iso-coumarin ring **XXIII**. The vinyl-iso-coumarin that had been formed could then be coupled to the para-methoxy-styrene through a cross-metathesis reaction. The final step would then be hydrogenation to remove the benzyl protecting groups as well as reducing the formed double bond. Unfortunately this synthetic pathway was halted at the directed ortho metalation reaction due to the low stability of the vinyl epoxide.

[16] (a) Yamato, M.; Hashigaki, K. *Chem. Pharm. Bull.* **1976**, *24*, 200-203. (b) Yamato, M. *Yakugaku Zasshi* **1959**, *79*, 1069-1073.
[17] Badaruddin, A. H.; Muhamma, A.; Hasan, R. N.; Aslam, M. M.; Shahid, M. *Chin. J. Chem.* **2007**, *25*, 102-104.
[18] Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933.

Indifferently of the choice of base, solvent or temperature of the reaction we were unable to trap the vinyl epoxide with the ortholithiated intermediate of **16**. We attribute this failure due to the instability of the vinyl epoxide. The ortho-lithiation was confirmed by trapping the lithiate with deuterated methanol to form the ortho-deuterated compound as well as by allyl bromide to form the ortho-allylated compound. To reduce the reactivity of the epoxide we attempted a cross-metathesis reaction of vinyl epoxide and para-methoxy-styrene (scheme 3. 18) to access epoxide **XXV**. However, the cross-metathesis reaction failed due to polymerization of the vinyl epoxide under these conditions. An alternative could be to do the cross-metathesis using the methyl-styrene of *para*-methoxy-styrene.



Scheme 3. 17. Planned synthetic route towards Agrimonol

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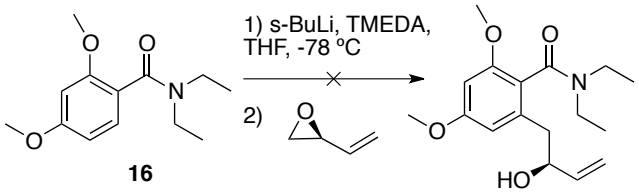
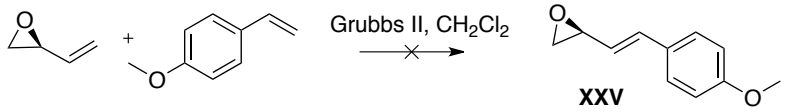


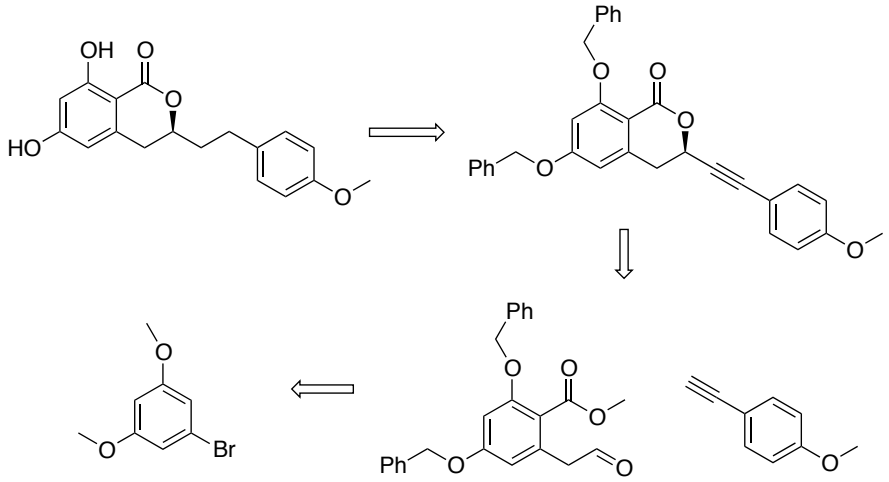
Scheme 3. 18. Unsuccessful trapping of ortho-metalated 16 with vinyl epoxide.



Scheme 3. 18. Attempted cross-metathesis of vinyl-epoxide and para-methoxy styrene.

We therefore proposed another route where the final compound would be generated after hydrogenation of the enantionselectively coupled para-methoxy phenyl acetylene and the same aldehyde key intermediate as in the synthesis of Cladosporin (scheme 3. 19). We would use the well known procedure developed by the group of Carreira[19] employing $Zn(OTf)_2$ and chiral *N*-dimethyl-ephedrine as ligand. The aldehyde would be formed in the same manner as had been done for Cladosporin.

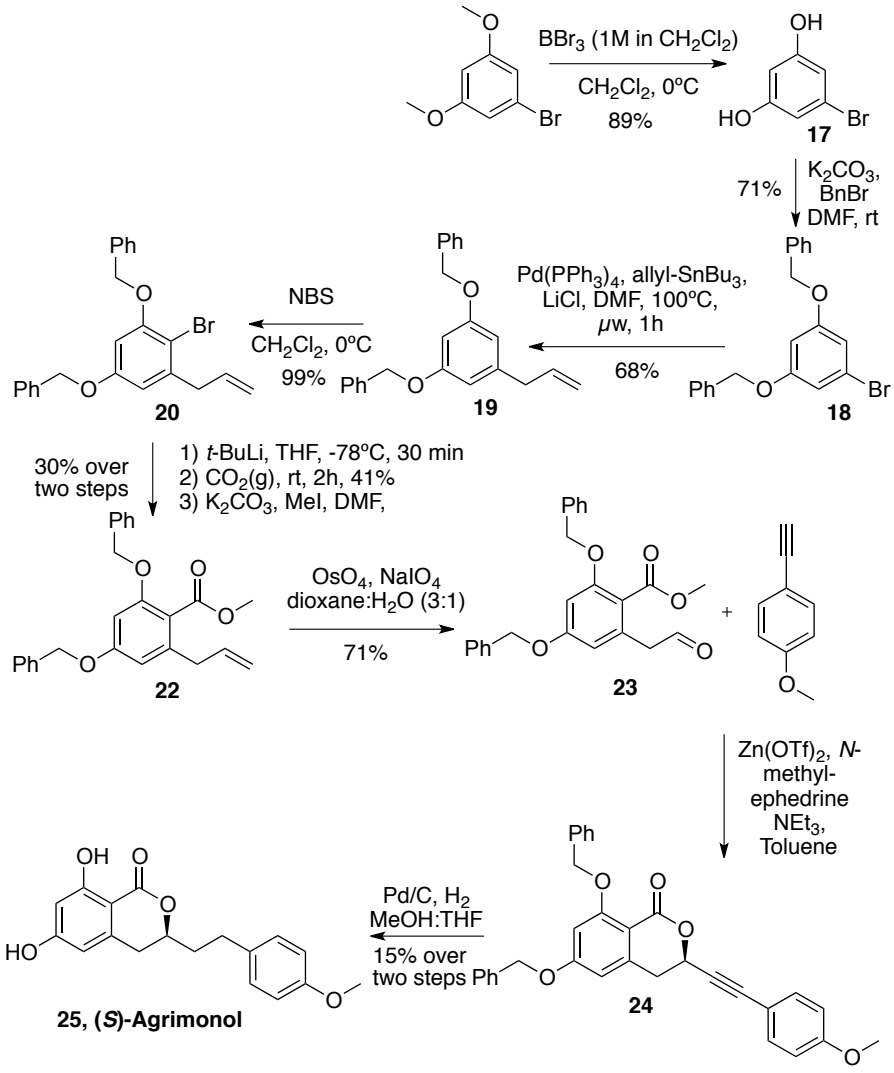
[19] Frantz, D. E.; Fässler, R.; Carreira, E. M., *J. Am. Chem. Soc.* **2000**, *122*, 1806-1807.



Scheme 3. 19. Retrosynthetic plan of new strategy towards Agrimonol.

Since one of the aryl rings in Agrimonol is substituted with a methoxy ether, it was necesseray to remove the methoxy ethers present in the commercially available 3,5-dimethoxy-bromobenzene that we wanted to start with, before coupling the two parts together. Thus, we could cleave the chosen protecting groups selectively when reaching the final step of the synthesis. Bearing this in mind, we started the synthesis with cleavage of the methyl ethers of 3,5-dimethoxy-bromobenzene using BBr_3 in CH_2Cl_2 at 0ºC over 2 days. The deprotected bromophenol (**17**) was then reacted with K_2CO_3 and benzyl bromide to form the corresponding 3,5-dibenzyloxy-bromobenzene (**18**). The bromide was then exchanged for an allyl substituent through a Stille coupling with allyl tributyltin. The allylsubstituted aryl **19** was then brominated in the ortho position to the allyl substitutent utilizing NBS at 0ºC. The reaction selectively gives bromination in this position after 1-2h rection time. Notably, if the reaction was stirred for a longer period of time in presence of a slight excess of NBS, further bromination was observed on the aryl ring. The bromide (**20**) was then reacted in the presence of *t*-BuLi in a lithium halogen exchange reaction and the lithium salt was reacted with CO_2 gas to form the carboxylic acid after acidic work up, in moderate yield. The desired acid

(**21**) undergoes a standard esterification after treatment with K_2CO_3 and MeI giving thus the ester (**22**) in good yield. The terminal double bond of the allyl substituent was then oxidized using the same conditions as for Cladosporin giving the aldehyde intermediate (**23**) in good yield. The aldehyde was then reacted in an enantioselective zink addition using $Zn(OTf)_2$ and (+)-*N*-methyl-ephedrine with the para-methoxy-phenyl acetylene.[19] The triple bond is then subsequently reduced under standard conditions using Pd/C under a H_2 atmosphere. We were pleased to see that this step also removes the benzyl ethers selectively and directly give access to the final compound (**25**). The reaction was found to proceed with a selectivity of 4:1 for the *S*-enantiomer after analysis by chiral HPLC. The synthesis is currently underway to produce more material for chiral separation by preparative HPLC to fully characterize the enantiopure product.



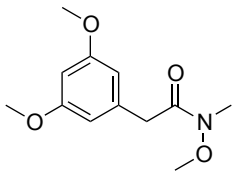
Scheme 3. 20. Total synthesis of (-)-Agrimonol.

In conclusion we have developed a highly convergent and facile route towards natural compound Agrimonol using a zinc catalyzed alkynylation reaction as our key transformation and ultimate coupling of the two fragments. The synthesis was completed in 8 steps giving the final product in 0.8% yield. This synthesis gives an open door towards the synthesis of natural compound Cladosporin as well as analogues bearing the same iso-coumarin scaffolds.

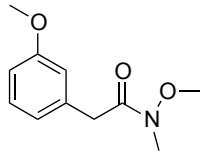
Experimental part

General methods

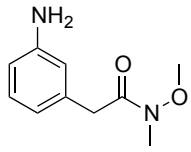
Unless specified all reactions were run under an atmosphere of Ar using anhydrous solvents. Thin layer chromatography was carried out using TLC aluminium sheets with 0.2 mm of silica gel (Polygram Sil G). Chromatographic purifications were carried out using a Biotage Isolera Flash Purification system over 10-100 g Silica cartridges (Snap Ultra). NMR spectra were recorded at 23°C on a Bruker Avance 400 Ultrashield apparatus. UPLC spectra were recorded on a Waters Acquity H-class UPLC/SQD spectrometer (Single Quadrupole Detecter, Electro Spray Ionization).



2-(3,5-dimethoxyphenyl)-N-methoxy-N-methylacetamide (1): 3,5-dimethoxybenzoic acid (1000 mg, 5.10 mmol), DIPEA (3.56 ml, 20.39 mmol) and EDC·HCl (977.00 mg, 5.10 mmol) were mixed in a 25 mL round bottomed flask in 17.0 mL CH_2Cl_2 at rt and stirred for 10 min. N, O-Dimethylhydroxylamine hydrochloride (994.00 mg, 10.19 mmol) was then added and the reaction was stirred over night. The reaction was then quenched with addition of a saturated solution of NH4Cl. The two phases were separated and the organic phase was washed with brine, dried under MgSO4 and concentrated by rotary evaporation. The crude residue was then redissolved in a small amount of EtOAc and concentrated on to Isolute for chromatography. Purification was made on a Biotage system over a 25g Silica cartridge (ISOLUTE) using EtOAc and heptane as eluent (gradient from 0-100% EtOAc) giving the product as a colourless oil in 59% yield (730.00 mg, 3.05 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.43-6.51 (m, 2 H), 6.36 (t, *J* = 2.4 Hz, 1H), 3.75-3.83 (m, 6H), 3.71 (s, 2H), 3.56-3.66 (m, 3H), 3.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 172.1, 160.7, 137.0, 107.3, 98.9, 61.3, 55.3, 39.6, 32.2. UPLC/ESI MS: R.T 0.90, MS m/z 240.0 [M+H].

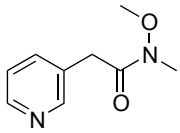


N-methoxy-2-(3-methoxyphenyl)-N-methylacetamide (2): 2-(3-methoxyphenyl)acetic acid (300.0 mg, 1.805 mmol) and EDC·HCl (519.0 mg, 2.71 mmol) were mixed in 10 mL CH_2Cl_2. DIPEA (1.26 mL, 7.22 mmol) was added and the mixture was stirred for 10 min followed by the addition of N,O-Dimethylhydroxylamin hydrochloride (528.0 mg, 5.42 mmol). The reaction was then left stirring at rt until starting material had been consumed (TLC) and was quenched with addition of a saturated solution of NH_4Cl. The two phases were separated and the organic phase was washed with brine, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was then redissolved in a small amount of EtOAc and concentrated on to Isolute for chromatography. Purification was made on a Biotage system over a 10g Silica cartridge (ISOLUTE) using EtOAc and heptane as eluent (gradient from 0-100% EtOAc) giving the product as a colourless oil in 65% yield (245.8 mg, 1.175 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.88-6.98 (m, 2H), 6.83 (dd, J = 8.3, 2.4 Hz, 1H), 3.75-3.89 (m, 5H), 3.65 (s, 3H), 3.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 172.2, 159.6, 136.4, 129.4, 121.6, 114.8, 112.3, 61.3, 55.1, 39.4, 32.2. UPLC/ESI MS: R.T 0.89, MS m/z 210.0 [M+H].

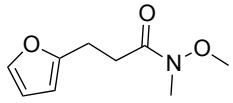


2-(3-aminophenyl)-N-methoxy-N-methylacetamide (3): 2-(3-aminophenyl)acetic acid (100 mg, 0.662 mmol) was dissolved in 2.5 mL CH_2Cl_2 and DIPEA (0.462 mL, 2.65 mmol) was added at rt. EDC·HCl (190 mg, 0.992 mmol) was added in one go and the mixture was left stirring for 10 min at rt. N,O-Dimethylhydroxylamin hydrochloride (194 mg, 1.985 mmol) was then added and the mixture was left stirring at rt until starting material had been consumed (TLC). The reaction was then quenched with addition of a saturated solution of NH_4Cl. The two phases were separated and the organic phase was washed with brine, dried under MgSO4 and concentrated by rotary evaporation. The crude residue was then redissolved in a small amount of EtOAc and concentrated on to Isolute for chromatography. Purification was made on a Biotage system over a 25g Silica cartridge (ISOLUTE) using EtOAc and heptane as eluent (gradient from 0-100% EtOAc) giving the product as a colourless oil in 16% yield (20.00 mg, 0.103

mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.10 (t, *J* = 7.8 Hz, 1H), 6.65-6.73 (m, 2H), 6.52-6.64 (m, 1H), 3.69 (s, 2H), 3.61 (s, 3H), 3.50 (bs, 2H), 3.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 146.1, 136.0, 129.4, 119.8, 116.0, 113.8, 61.3, 39.3, 32.2. UPLC/ESI MS: R.T 0.66, MS m/z 195.0 [M+H].

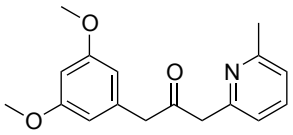


N-methoxy-N-methyl-2-(pyridin-3-yl)acetamide (4): 2-(pyridin-3-yl)acetic acid (100.0 mg, 0.729 mmol) was dissolved in 2.5 mL CH_2Cl_2 and DIPEA (0.509 mL, 2.92 mmol) was added at rt. EDC·HCl (140 mg, 0.729 mmol) was added in one go and the mixture was left stirring for 10 min at rt. N,O-dimethylhydroxylamine (142 mg, 1.458 mmol) was then added and the mixture was left stirring at rt until all starting material had been consumed (TLC). The reaction was quenched with addition of a saturated solution of NH_4Cl. The two phases were separated and the organic phase was washed with brine, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was then redissolved in a small amount of EtOAc and concentrated on to Isolute for chromatography. Purification was made on a Biotage system over a 10g Silica cartridge (ISOLUTE) using EtOAc and heptane as eluent (gradient from 0-100% EtOAc) giving the product as a colourless oil in 26% yield (34.0 mg, 0.189 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.41-8.59 (m, 2H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 5.0 Hz, 1H), 3.78 (s, 2H), 3.69 (s, 3H), 3.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 171.4, 150.3, 148.0, 137.2, 130.7, 123.4, 61.4, 36.3, 32.3. UPLC/ESI MS: R.T 0.48, MS m/z 181.0 [M+H].

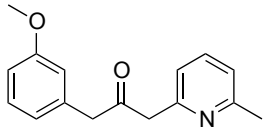


3-(furan-2-yl)-N-methoxy-N-methylpropanamide (5): 3-(furan-2-yl)propanoic acid (100.0 mg, 0.714 mmol) was put into a dry μw vial. The system was purged with argon and 2.5 mL of CH_2Cl_2 was added followed by DIPEA (0.499 ml, 2.85 mmol). The solution was cooled down to 0°C and HATU (407.0 mg, 1.070 mmol) was added.. The mixture was left stirring for 1h at 0°C and then N, O-Dimethylhydroxylamine hydrochloride (77 mg, 0.785 mmol) was added in one go. The mixture was left stirring over night slowly warming to rt. The reaction was quenched with addition of a saturated solution of NH_4Cl. The two phases were separated and the organic

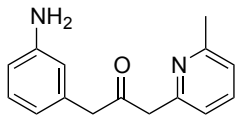
phase was washed with brine, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was then redissolved in a small amount of EtOAc and concentrated on to Isolute for chromatography. Purification was made on a Biotage system over a 10g Silica cartridge (ISOLUTE) using EtOAc and heptane as eluent (gradient from 0-100% EtOAc) giving the product as a colourless oil in 75% yield (98.0 mg, 0.535 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30 (bs, 1H), 6.27 (bs, 1H), 6.02 (bs, 1H), 3.65 (s, 3H), 3.18 (s, 3H), 2.97 (t, J = 6.8 Hz, 2H), 2.77 (t, J = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 173.4, 154.9, 141.1, 110.3, 105.3, 61.3, 32.3, 30.5, 23.2. UPLC/ESI MS: R.T 0.87, MS m/z 184.0 [M+H].



1-(3,5-dimethoxyphenyl)-3-(6-methylpyridin-2-yl)propan-2-one (6): To a -78 °C solution of sec-butyllithium (1.194 mL, 1.672 mmol) in 4 mL of THF was added 2,6-lutidine (0.195 mL, 1.672 mmol) and was left stirring at -78 °C for about 2 min. To the solution was then added (**1**) (200 mg, 0.836 mmol) in 4 mL THF. The reaction was left stirring until all starting material had reacted (LCMS, TLC) and was then quenched by additon of EtOAc followed by a saturated solution of NH_4Cl when at room temperature. The two phases were separated and the organic phase was washed with brine, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was then redissolved in a small amount of EtOAc and concentrated on to Isolute for chromatography. Purification was made on a Biotage system over a 10g Silica cartridge (ISOLUTE) using EtOAc and heptane as eluent (gradient from 0-100% EtOAc) giving the product as yellow oil in 93% yield (223.0 mg, 0.782 mmol). Selected signals of ketone, compound interchanges between keto-enol form. ^{1}H NMR (400 MHz, DMSO-*d*) δ ppm 7.61 (t, J = 7.8 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H), 6.37 (bs, 1H), 6.34 (bs, 2H), 3.93 (s, 2H), 3.76 (s, 2H), 3.70 (s, 6H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*d*) δ ppm 204.7, 168.7, 160.3, 157.3, 154.3, 140.0, 138.2, 136.7, 121.4, 121.1, 107.7, 98.5, 95.00, 55.1, 50.9, 48.9, 23.9. UPLC/ESI MS: R.T 0.89, MS m/z 286.0 [M+H].

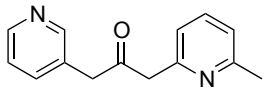


1-(3-methoxyphenyl)-3-(6-methylpyridin-2-yl)propan-2-one (7): sec-butyllithium (171 µl, 0.239 mmol) was added to -78°C solution of 0.5 mL of THF in a schlenck. To this solution was added dropwise Lutidine (27.8 µl, 0.239 mmol) and the reaction changed from light yellow colour to deep red. After two minutes stirring at -78°C, **2** (25 mg, 0.119 mmol) in 0.5 mL THF was added. The reaction was followed by LCMS and showed consumtion of SM within 15 min. The solution was then quenched by additon of EtOAc followed by a saturated solution of NH_4Cl when at room temperature. The two phases were separated and the organic phase was washed with brine, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was then redissolved in a small amount of EtOAc and concentrated on to Isolute for chromatography. Purification was made on a Biotage system over a 10g Silica cartridge (ISOLUTE) using EtOAc and heptane as eluent (gradient from 0-100% EtOAc) giving the product as yellow oil in 89% yield (27.0 mg, 0.106 mmol). Selected signals of ketone, compound interchanges between keto-enol form. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.52 (t, J = 7.9 Hz, 1H), 7.22 (dd, J = 7.5 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 6.79 (m, 2H), 6.74 (m, 1H), 3.92 (s, 2H), 3.79 (s, 2H), 3.78 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 204.9, 172.1, 159.8, 158.2, 153.8, 139.9, 137.6, 129.6, 121.9, 117.7, 115.1, 112.7, 94.5, 55.2, 49.2, 24.4. UPLC/ESI MS: R.T 0.87, MS m/z 256.0 [M+H].

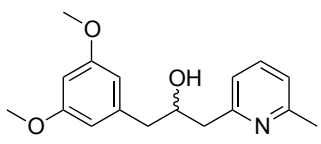


1-(3-aminophenyl)-3-(6-methylpyridin-2-yl)propan-2-one (8): To a -78°C solution of sec-butyllithium (147 µl, 0.206 mmol) in 0.5 mL THF was added 2,6-lutidine (23.99 µl, 0.206 mmol) and was left stirring at -78°C for about 2 min. To the solution was then added **3** (20 mg, 0.103 mmol) in 0.5 mL THF. The reaction was left stirring until all starting material had reacted (LCMS, TLC) and was then quenched by additon of EtOAc followed by a saturated solution of NH_4Cl when at room temperature. The two phases were separated and the organic phase was washed with brine, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was then redissolved in a small amount of EtOAc and concentrated on to Isolute for chromatography. Purification was made on a Biotage system over a 10g Silica cartridge (ISOLUTE) using EtOAc and heptane as eluent (gradient from 0-

100% EtOAc) giving the product as yellow oil in 45% yield (11.0 mg, 0.046 mmol). Selected signals of ketone, compound interchanges between keto-enol form. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.48 (t, J = 7.5 Hz, 1H), 7.04 (m, 2H), 6.96 (d, J = 7.8 Hz, 1H), 6.57 (m, 2H), 6.53 (bs, 1H), 3.92 (s, 2H), 3.71 (s, 2H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 205.2, 172.4, 158.1, 153.9, 151.9, 146.9, 129.8, 121.8, 119.9, 116.3, 114.0, 98.6, 50.1, 24.3, 14.3. UPLC/ESI MS: R.T 0.63, MS m/z 241.0 [M+H].

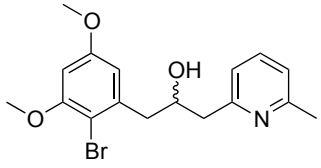


1-(6-methylpyridin-2-yl)-3-(pyridin-3-yl)propan-2-one (9): sec-butyllithium (174 µl, 0.244 mmol) was added to -78 °C solution of 0.5 mL of THF in a schlenck. To this solution was added dropwise lutidine (28.4 µl, 0.244 mmol) and the reaction changed from light yellow colour to deep red. After two minutes stirring at -78 °C, **4** (22 mg, 0.122 mmol) in 0.5 mL THF was added. The reaction was followed by LCMS and showed consumtion of SM within 15 min. The solution was then quenched by additon of EtOAc followed by a saturated solution of NH_4Cl when at room temperature. The two phases were separated and the organic phase was washed with brine, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was then redissolved in a small amount of EtOAc and concentrated on to Isolute for chromatography. Purification was made on a Biotage system over a 10g Silica cartridge (ISOLUTE) using EtOAc and heptane as eluent (gradient from 0-100% EtOAc) giving the product as yellow oil in 36% yield (10.0 mg, 0.044 mmol). Selected signals of ketone, compound interchanges between keto-enol form. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.48 (m, 2H), 7.66 (m, 1H), 7.52 (m, 1H), 7.24 (m, 1H), 7.06 (d, J = 7.9 Hz, 1H), 6.96 (d, J = 7.9 Hz, 1H), 3.95 (s, 2H), 3.85 (s, 2H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 204.0, 172.4, 153.6, 150.7, 148.5, 137.9, 137.2, 123.5, 121.9, 117.8, 94.3, 52.3, 49.3, 24.5. UPLC/ESI MS: R.T 0.50, MS m/z 227.0 [M+H].

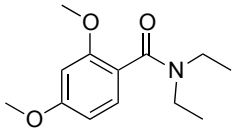


1-(3,5-dimethoxyphenyl)-3-(6-methylpyridin-2-yl)propan-2-ol (11): **6** (30.0 mg, 0.105 mmol) was

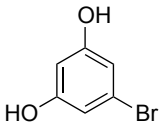
dissolved in 1 mL dry THF and cooled down to 0°C. BH_3·THF (210.0 µl, 0.210 mmol) was added dropwise (bubbling visible) and the solution was left stirring for about 1h (consumation of sm was followed by LCMS, TLC). The reaction was quenched by addition of EtOAc followed by water. The two phases were separated and the organic phase was washed with brine, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was then redissolved in a small amount of EtOAc and concentrated on to Isolute for chromatography. Purification was made on a Biotage system over a 10g Silica cartridge (ISOLUTE) using EtOAc and heptane as eluent (gradient from 0-100% EtOAc) giving the product as yellow oil in 54% yield (16.0 mg, 0.057 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.50 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.91 (d, J = 7.4 Hz, 1H), 6.41 (m, 2H), 6.33 (m, 1H), 4.27 (m, 1H), 3.78 (s, 6H), 2.93-2.69 (m, 4H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 160.9, 159.4, 157.3, 141.2, 137.4, 121.3, 120.9, 107.6, 98.5, 72.1, 55.4, 44.1, 41.9, 24.3. UPLC/ESI MS: R.T 0.73, MS m/z 288.0 [M+H].



1-(2-bromo-3,5-dimethoxyphenyl)-3-(6-methylpyridin-2-yl)propan-2-ol (12): **6** (20 mg, 0.070 mmol) was dissolved in 0.7 mL dry CH_2Cl_2 and cooled down to 0°C. NBS (13.01 mg, 0.073 mmol) was added and the reaction was stirred for 1h or until SM was consumed. The reaction was then diluted with EtOAc and water was added. The two phases were separated and the organic phase was washed with brine, dried under $MgSO_4$ and concentrated by rotary evaporation. No further purification was made, product contained no byproducts, 86% yield (22.0 mg, 0.060 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.50 (t, J = 7.4 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 6.91 (d, J = 7.4 Hz, 1H), 6.53 (d, J = 2.3 Hz, 1H), 6.38 (d, J = 2.3 Hz, 1H), 4.38 (m, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.03 (d, J = 6.9 Hz, 2H), 2.92-2.89 (m, 2H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 159.3, 159.1, 156.8, 155.8, 140.2, 137.5, 121.3, 120.8, 108.0, 106.6, 105.4, 98.1, 95.5, 70.7, 55.6, 43.9, 41.8. UPLC/ESI MS: R.T 0.81, MS m/z 367.0 [M+H].



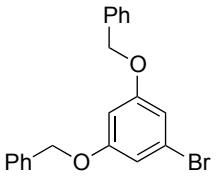
N,N-diethyl-2,4-dimethoxybenzamide (16): 2,4-dimethoxybenzoic acid (547.0 mg, 3.00 mmol) and DIPEA (2.098 mL, 12.01 mmol) was dissolved in 10 mL CH_2Cl_2 and cooled down to 0°C. HATU (2.28 g, 6.01 mmol) was added and the reaction was stirred at rt for 1h. Diethylamine (0.624 mL, 6.01 mmol) was then added and the reaction was stirred over night. The solution was then quenched by additon of NH_4Cl. The two phases were separated and the organic phase was washed with brine, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was then redissolved in a small amount of EtOAc and concentrated on to Isolute for chromatography. Purification was made on a Biotage system over a 25g Silica cartridge (ISOLUTE) using EtOAc and heptane as eluent (gradient from 0-100% EtOAc) giving the product as yellow oil in 121% yield (864.0 mg, 3.64 mmol). The product contains a byproduct that can be removed by dissolving it in $CHCl_3$ which crashes out a white solid that can be filtered off, pure product 700.0 mg, 2.95 mmol. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.10 (d, J = 8.5 Hz, 1H), 6.48 (d, J = 8.5 Hz, 1H), 6.44 (bs, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.53 (bs, 2H), 3.14 (q, J = 14.2, 7.0 Hz, 2H), 1.22 (t, J = 7.0 Hz, 3H), 1.02 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 168.9, 161.3, 156.7, 128.5, 119.9, 104.7, 98.8, 55.6, 42.9, 39.0, 38.7, 14.1, 13.0. UPLC/ESI MS: R.T 0.93, MS m/z 238.0 [M+H]. Experimental data in correlation with previously described synthesis[20].



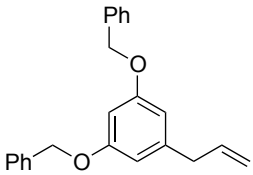
5-bromobenzene-1,3-diol (17): To a solution of 3,5-dimethoxy-bromobenzene (4.0 g, 18.5 mmol) in CH_2Cl_2 (61 mL) at 0°C was added BBr_3 (40.5 mL, 40.5 mmol, 1M in CH_2Cl_2). The reaction was followed by TLC until all starting material had been deprotected. Water was then added and the two phases were separated. The aqeous phase was washed several times with EtOAc and the organic fractions were combined, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was purified by column chromatography on a Biotage system over a 100 g Silica cartridge (ISOLUTE). The product was obtained as a white solid in 89% yield (3.1 g, 18.4

[20] Tan, J. S.; Ciufolini, M. A., *Org. Lett.* **2006**, *8*, 4471-4774.

mmol). ^{1}H NMR (400 MHz, DMSO-*d*) δ ppm 9.62 (s, 2H), 6.37 (d, J = 2.2 Hz, 2H), 6.18 (t, J = 2.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-*d*) δ ppm 159.4, 121.8, 109.4, 101.8. UPLC/ESI MS: R.T 0.77, MS m/z 190.0 [M+H].

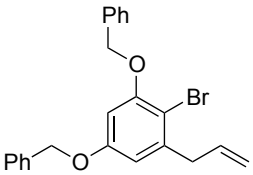


3,5-dibenzyloxo-bromobenzene (18): To 5-bromobenzene-1,3-diol (**17**) (3.0 g, 15.9 mmol) in DMF (132 mL) was added K_2CO_3 (8.7 g, 63.5 mmol) followed by benzyl bromide (7.5 mL, 63.5 mmol). The reaction was stirred until all starting material had been protected (TLC, LCMS). The reaction was quenched by addition of water and EtOAc. The two phases were separated and the organic phase was washed several times with brine, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was purified by column chromatography on a Biotage system over a 100 g Silica cartridge (ISOLUTE). The product was isolated as a beige solid in 71% yield (4.2 g, 11.3 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.39-7.33 (m, 10H), 6.77 (d, J = 2.2 Hz, 2H), 6.53 (t, J = 2.2 Hz, 1H), 5.00 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 160.5, 136.4, 128.8, 128.3, 127.7, 123.1, 111.2, 101.5, 70.4. UPLC/ESI MS: R.T 1.40, MS m/z 370.0 [M+H].

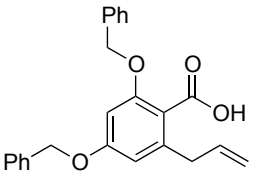


1,3-dibenzyloxo-5-allyl-benzene (19): 3,5-dibenzyloxo-bromobenzene (**18**) (1.0 g, 2.7 mmol) was dissolved in dry DMF (27 mL) in two microwave vials. To the solution was then added allyltributyl tin (1.0 mL, 3.5 mmol), palladium tetrakis triphenylphosphine (313.0 mg, 0.271 mmol) and lithium chloride (344.0 mg, 8.1 mmol) in that order. The vials were sealed and heated to 100°C over 1h under microwave conditions. The reaction was then quenched by the addition of water and EtOAc and the two phases were separated. The organic phase was washed several times with brine and dried over $MgSO_4$. The solution was then filtered through a pad of silica eluting with EtOAc:heptane (1:1) before it was concentrated by rotary evaporation. The crude residue was then purified by column chromatography on a Biotage system over a 50 g Silica cartridge (ISOLUTE). The product was isolated in 90% yield (800 mg, 2.4 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.39-7.30 (m, 10H), 6.49-6.47 (m,

3H), 6.00-5.89 (m, 1H), 5.13-5.06 (m, 2H), 5.02 (s, 4H), 3.33 (d, J = 6.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 160.1, 142.6, 137.1, 128.7, 128.4, 128.1, 127.7, 116.2, 107.9, 99.8, 70.1, 40.6. UPLC/ESI MS: R.T 1.39, MS m/z 331.0 [M+H].

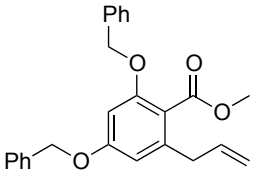


1,3-bis(benzyloxy)-4-bromo-5-allyl-benzene (20): 1,3-dibenzyloxo-5-allyl-benzene (**19**) (895 mg, 2.71 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled down to 0°C. N-bromosuccinimide (482 mg, 2.71 mmol) was then added and the reaction was stirred until all starting material had been brominated (TLC, LCMS). Upon completion the reaction was quenched with addition of water. The two phases were separated and the organic phase was washed several times with brine, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was purified by column chromatography on a Biotage system over a 25 g Silica cartridge (ISOLUTE). The pure product was isolated in 99% yield (1.1 g, 2.69 mmol) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.48-7.30 (m, 10H), 6.54 (d, J = 2.7 Hz, 1H), 6.50 (d, J = 2.7 Hz, 1H) 6.02-5.91 (m, 1H), 5.14-5.07 (m, 4H), 5.00 (s, 2H), 3.53 (d, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 158.7, 156.0, 141.7, 136.7, 135.6, 128.8, 128.7, 128.3, 128.0, 127.7, 127.1, 116.8, 108.4, 106.0, 100.2, 71.0, 70.4, 40.8. UPLC/ESI MS: R.T 1.45, MS m/z 410.0 [M+H].

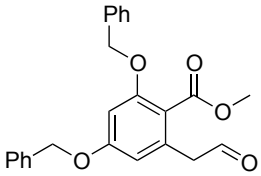


2-allyl-4,6-bis(benzyloxy)benzoic acid (21): 1,3-bis(benzyloxy)-4-bromo-5-allyl-benzene (**20**) (1.0 g, 2.44 mmol) was dissolved in dry THF (10 mL) and cooled down to -78°C. *tert*-BuLi (1.5 mL , 2.69 mmol, 1.7M in pentane) was then added and the reaction was stirred at this temperature for 30 min. The cooling bath was then removed and CO_2 gas was then bubbled through the solution for 1h. The reaction was then acidified by addition of 5 mL of 1M HCl solution. The two phases were separated and the organic phase was washed several times with brine, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was purified by column chromatography on a Biotage system over a

50 g Silica cartridge (ISOLUTE). The pure product was isolated in 41% yield (376 mg, 1.0 mmol) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.42-7.32 (m, 10H), 6.55 (d, J = 2.2 Hz, 1H), 6.52 (d, J = 2.2 Hz, 1H) 6.02-5.91 (m, 1H), 5.13 (s, 2H), 5.11-5.04 (m, 2H), 5.05 (s, 2H), 3.65 (d, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 168.7, 161.5, 158.6, 144.9, 136.8, 136.2, 135.6, 128.9, 128.8, 128.6, 128.4, 127.7, 127.5, 116.4, 113.5, 109.5, 99.2, 71.7, 70.3, 39.0. UPLC/ESI MS: R.T 1.20, MS m/z 375.0 [M+H].

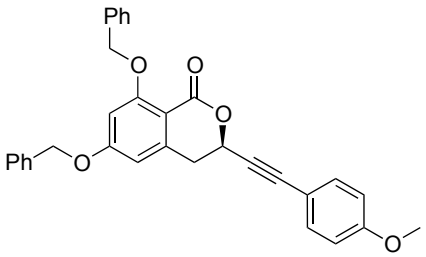


Methyl 2-allyl-4,6-bis(benzyloxy)benzoate (22): 2-allyl-4,6-bis(benzyloxy)benzoic acid (**21**) (1.0 g, 2.67 mmol) was dissolved in DMF (9 mL) and K_2CO_3 (554.0 mg , 4.01 mmol) was added followed by MeI (0.84 mL, 13.35 mmol). The reaction was monitored by TLC and upon completion the reaction was quenched by addition of water. The two phases were separated and the organic phase was washed several times with brine, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was purified by column chromatography on a Biotage system over a 50 g Silica cartridge (ISOLUTE). The pure product was isolated in 71% yield (740.0 mg, 1.9 mmol) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38-7.28 (m, 10H), 6.46 (s, 2H), 5.95-5.85 (m, 1H), 5.10-5.08 (m, 2H), 5.05 (s, 2H), 5.02 (s, 2H), 3.85 (s, 3H), 3.38 (d, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 168.6, 160.7, 157.4, 140.5, 136.8, 136.58, 136.6, 128.7, 128.6, 128.4, 128.3, 127.9, 127.7, 127.0, 117.1, 116.5, 107.7, 99.0, 70.6, 70.2, 52.1, 38.1. UPLC/ESI MS: R.T 1.34, MS m/z 389.0 [M+H].

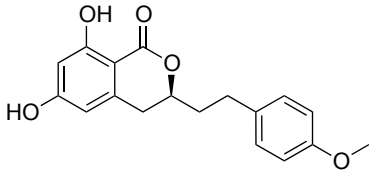


Methyl 2,4-bis(benzyloxy)-6-(2-oxoethyl)benzoate (23): Methyl 2-allyl-4,6-bis(benzyloxy)benzoate (**22**) (332.0 g, 0.85 mmol) was dissolved in dioxane:water (3:1, 21mL). 2,6-Lutidine (0.20 mL, 1.7 mmol) and OsO4 (1.0 mL, 0.085 mmol, 2.5wt% in *t*-BuOH) were added and the reaction was stirred in the absence of light at room temperature for 1h. $NaIO_4$ (548.0 mg, 2.56 mmol) was then added and the reaction was left stirring for 4h. Water and CH_2Cl_2 was added and the two phases were separated. The organic phase was washed

several times with water, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was purified by column chromatography on a Biotage system over a 25 g Silica cartridge (ISOLUTE). The pure product was isolated in 71% yield (237.0 mg, 0.61 mmol) as a black oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.68 (t, J = 1.8 Hz, 1H), 7.38-7.30 (m, 10H), 6.55 (d, J = 2.2 Hz, 1H), 6.42 (d, J = 2.2 Hz, 1H), 5.07 (s, 2H), 5.03 (s, 2H), 3.84 (s, 3H), 3.67 (d, J = 1.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 190.2, 169.9, 161.0, 157.6, 136.0, 135.9, 128.9, 128.8, 128.5, 128.2, 127.7, 127.0, 118.6, 106.7, 106.7, 71.0, 70.7, 52.8. UPLC/ESI MS: R.T 1.24, MS m/z 391.0 [M+H].



(*R*)-6,8-bis(benzyloxy)-3-((4-methoxyphenyl)ethynyl)isochroman-1-one (24): $Zn(OTf)_2$ (100.0 mg, 0.28 mmol) and (+)-N-methyl ephedrine (55.0 mg, 0.30 mmol) were placed in a 5 mL vial and purged with argon for 15 min. Toluene (0.5 mL) and Et_3N (43 µL, 0.30 mmol) was added and the heterogeneous mixture was stirred at room temperature for 2h. 1-ethynyl-4-methoxybenzene (40 µL, 0.30 mmol) was added and the reaction was stirred for 15 min at which point methyl 2,4-bis(benzyloxy)-6-(2-oxoethyl)benzoate (**23**) (100 mg, 0.26 mmol) was added. The reaction was monitored by TLC and when all aldehyde had been consumed the reaction was quenched with addition of sat. NH_4Cl solution. The two phases were separated and the organic phase was washed with water followed by brine, dried under $MgSO_4$ and concentrated by rotary evaporation. The crude residue was purified by column chromatography on a Biotage system over a 10 g Silica cartridge (ISOLUTE). The product was used as such without further purification.



(*S*)-6,8-dihydroxy-3-(4-methoxyphenethyl)isochroman-1-one (25): (*R*)-6,8-bis(benzyloxy)-3-((4-methoxyphenyl)ethynyl)isochroman-1-one (**24**) (31.0 mg, 0.063 mmol) was dissolved in MeOH:THF (300 µL, 1:1). Pd/C (6.7 mg, 0.0063 mmol) was added and an atmosphere of H_2 was generated. The reaction was stirred until all starting material had been consumed (TLC, LCMS). Upon completion the reaction was diluted with EtOAc and filtered through a pipette filled with SiO2. The filtered solution was concentrated and purified by column chromatography on a Biotage system over 10 g silica cartridge. The product was obtained as a white solid in 23% yield (4.5 mg, 0.014 mmol). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.14 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 8.3 Hz, 2H), 6.20 (bs, 2H), 4.50-4.44 (m, 1H), 3.75 (s, 3H), 2.87 (d, J = 6.9 Hz, 2H), 2.84-2.61 (m, 2H), 2.10-1.95 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ ppm 171.6, 166.3, 165.6, 159.5, 143.5, 134.4, 130.4, 114.9, 107.9, 102.1, 101.6, 79.9, 55.6, 37.8, 33.9, 31.1. UPLC/ESI MS: R.T 1.05, MS m/z 315.0 [M+H]. Spectroscopic data are in accordance to previously reported results.[21]

[21] Kato, H.; Li, W.; Koike, M.; Wang, Y.; Koike, K., *Phytochem.* **2010**, *71*, 1925-1929.