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Application of the Metal-Catalyzed Rearrangement of Propargyl Acetates to the Total Synthesis of Natural Products of the Neomerane Family

Application in Catalysis of New Secondary Phosphine Oxide- and NHC-Capped Cyclodextrin-Gold(I) Complexes

Coralie Tugny

*Méthodes Appliquées en Chimie Organique (MACO) team
Institut Parisien de Chimie Moléculaire (IPCM)*

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Publicly defended on the 13th of November 2015
In front of an examining board consisting of:

Laurent Micouin, DR
Patrick Pale, PR
Olivier Mirguet, DR
Matthieu Sollogoub, PR
Jean-Philippe Goddard, PR
Virginie Mouriès-Mansuy, DR
Louis Fensterbank, PR

Université Paris Descartes - LCBPT
Université de Strasbourg - LASYROC
Institut de Recherches Servier
Université Pierre et Marie Curie - IPCM
Université de Haute-Alsace - COB
Université Pierre et Marie Curie - IPCM
Université Pierre et Marie Curie - IPCM

Rapporteur
Rapporteur

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Abbreviations and Acronyms

Ac	Acetyl
Bp	Boiling Point
Bn	Benzyl
calcd	calculated
CI	Chemical Ionisation
COSY	Correlation Spectroscopy
Cp	Cyclopentadienyl
DCM	DiChloroMethane
DCE	DiChloroEthane
Dec.	Decomposition
DIPEA	Di- <i>iso</i> -PropylEthylAmine
disp.	dispersed
DMAP	DiMethylAminoPyridine
DMF	DiMethylFormamide
DMSO	DiMethylSulfOxide
DNPH	DiNitroPhenylHydrazine
<i>dr</i>	<i>diastereomeric ratio</i>
equiv.	equivalent
ee	enantiomeric excess
Et	Ethyl
EWG	Electron-Withdrawing
F	Fusion point
HBHC	Hydrogen Bond Heterocyclic Carbene

HMPT	HexaMethylPhosphoTriamide
HRMS	High Resolution Mass Spectroscopy
IPCM	Institut Parisien de Chimie Moléculaire
IR	InfraRed
LG	Leaving Group
LRMS	Low Resolution Mass Spectroscopy
LUMO	Lowest Unoccupied Molecular Orbital
M	Mol.L ⁻¹
Me	Methyl
MEM	MethoxyEthoxyMethyl ether
MOM	MethOxyMethyl
MS	Mass Spectroscopy
NAC	<i>N</i> -Acyclic Carbene
NALG	Nucleophile-Assisting Leaving Group
<i>n</i> -Bu	<i>normal</i> -Butyl
NHC	<i>N</i> -Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Enhancement Spectroscopy
<i>n</i> -Bu	<i>normal</i> Butyl
<i>n</i> -Pent	<i>normal</i> -Pentane
Nu ⁻	Nucleophile
<i>p</i>	<i>para</i>
PE	Petroleum Ether
Ph	Phenyl
Piv	Pivaloyl

PTSA	<i>Para</i> -TolueneSulfonic Acid
Quant.	Quantitative
rel.	relative
R_f	Retention factor
r.t.	room temperature
TBAF	Tetra- <i>n</i> -ButylAmmonium Fluoride
TBDPS	<i>tert</i> -ButylDiphenylSilyl
TBS	<i>tert</i> -ButyldimethylSilyl
<i>t</i> -Bu	<i>tert</i> -Butyl
Tf	Trifluoromethylsulfonate
TFA	trifluoroacetic acid
THF	TetraHydroFuran
TLC	Thin Layer Chromatography
TMS	TriMethylSilyl
TMSA	TriMethylSilylAcetylene
Ts	Tosyl

General Introduction

Elemental gold has an atomic number of 79 and an electron configuration of $[\text{Xe}]4f^{14}5d^{10}6s^1$, and the most prominent characteristics of the electronic structure of gold are the consequence of strong relativistic effects.¹ The latter are indeed crucial to understanding the electronic structure of heavy elements.

The term “relativistic effects” refers to the theory of relativity, and the need to consider the velocity of electrons as significant to the speed of light. One consequence of this theory is that mass increases towards infinity as a body’s velocity approaches c , and because the Bohr radius of an electron orbiting in a nucleus is inversely proportional to the mass of the electron, this increase in mass corresponds to a decrease in radius, that is the relativistic contraction of s and p orbitals.

In Au, the relativistic contraction of the 6s orbital result in greatly strengthened Au-L bonds, where L is the ligand. Other consequences of relativistic effects are:

-the phenomenon of aurophilicity,² that is the tendency for Au-Au interactions to be stabilizing on the order of hydrogen bonds;

-the large first ionization potential observed for Au (9.22 eV vs. 7.57 eV for Ag).

In addition, it seems that relativistic contraction of the valence 6s and 6p orbitals should be responsible for the superior Lewis acidity of cationic gold(I) species compared with other Group 11 metals because these orbitals correspond to a relatively low-lying LUMO and therefore strong acidity.

Au(I)^+ is a large, diffuse cation that shares positive charge with the phosphine ligand. Thus, one might expect orbital rather than charge interactions to dominate in binding a second ligand, so that phosphine- Au(I)^+ may be considered a soft Lewis acid preferentially activating soft electrophiles such as π -systems.

Studies on Au^+ -ethylene and Au^+ -ethyne bonding indicate $\sim 10 \text{ Kcal.mol}^{-1}$ greater stabilization for the ethylene complex over the ethyne complex.³ Because Au(I) apparently does not selectively complex alkynes over other π -systems, the phenomenon of alkynophilicity, that is

¹ Gorin, D.J., Toste, F.D. *Nature* **2007**, *446*, 395-403.

² Scherbaum, F., Grohmann, A., Huber, B., Krüger, C., Schmidbaur, H. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1544-1546.

³ Hertwig, R.H., *et al.* *J. Phys. Chem.* **1996**, *100*, 12253-12260; Nechaev, M.S., Rayon, V.M., Frenking, G. *J. Phys. Chem. A* **2004**, *108*, 3134-3142.

the superior reactivity of Au-alkyne complexes towards nucleophilic addition, may be due to discrimination by the nucleophile in selecting between Au(I)-activated electrophiles. Such selectivity can be understood by considering the relative energy levels of ethyne and ethylene LUMOs: alkynes have intrinsically lower HOMOs and LUMOs than the corresponding alkenes (by ~0.5 eV), and are therefore less nucleophilic and more electrophilic.⁴ It can therefore be expected that a Au-alkyne complex should have a lower LUMO for the addition of a nucleophile than an analogous Au-alkene complex.

Gold has come to be considered as an exceedingly mild Lewis acid and the vast majority of reactions developed with homogeneous Au catalysts has exploited the propensity of Au to activate carbon-carbon π -bonds as electrophiles.

Owing to the high gain in molecular complexity,⁵ exceptionally mild reaction conditions and high atom economy⁶ inherent to gold-catalyzed transformations, there has been a noticeable trend during the past decade towards the use of homogeneous gold-catalyzed transformations in the total synthesis of natural products.⁷

The present work aims at the valorization of the gold-catalyzed rearrangement of propargyl acetates in the total synthesis of small molecule sesquiterpene natural products of the neomerane family. On the other hand, the behaviour of new secondary phosphine oxide- and cyclodextrin-based gold(I) catalysts has been studied, with a view to achieve efficient tuning of the reactivity in gold catalysis.

The first part *Bibliographic Analysis* illustrates the successful application of various gold-catalyzed transformations to the total synthesis of terpenoid natural products (Chapter I) as well as the efforts made in the developments of new catalysts to improve the efficiency and/or selectivity of gold-catalyzed transformations (Chapter II).

Thus, the first chapter shows different reaction types, ranging from the simple Michael or Claisen reactions to more elaborated transformations leading to a significant gain in complexity such as propargyl esters and ethers migrations or cycloisomerization/ring expansion tandem reactions. In each case, the mode of activation of the substrate by the gold catalyst is discussed.

⁴ Fleming, I. *Frontier Orbitals and Organic Chemical reactions* (Wiley, Chichester, **1976**).

⁵ Bertz, S.H. *J. Am. Chem. Soc.* **1981**, *103*, 3599.

⁶ Trost, B.M. *Science* **1991**, *254*, 1471; Trost, B.M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259.

⁷ For reviews on the application of gold-catalysis in total synthesis, see: Hashmi, A.S.K., Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766-1775; Hashmi, A.S.K., Rudolph, M. *Chem. Soc. Rev.* **2012**, *41*, 2448-2462; Zhang, Y., Luo, T., Yang, Z. *Nat. Prod. Rep.* **2014**, *31*, 489-503.

The second chapter introduces the purpose of developing new ligands for gold catalysis and gives a number of representative examples of phosphines and carbenes developed to provide a handle to control the course of the gold-catalyzed transformations. This part is not intended to be exhaustive. In particular, the design of ligands and catalysts for enantioselective catalysis is not covered.

The second part *Present Work* is divided in three chapters.

The first chapter deals with the total syntheses of (\pm)-Valeneomerin B and (\pm)-Neomeranol. Firstly, the preparation of a common intermediate to the two natural products is presented. Then, the total synthesis of (\pm)-5-*epi*-Valeneomerin B and studies carried out toward the total synthesis of (\pm)-Valeneomerin B are reported. Lastly, efforts toward the total synthesis of (\pm)-Neomeranol are exposed.

The second chapter covers the preparation and application in catalysis of Secondary Phosphine Oxide (SPO)-gold(I) complexes.

Finally, the third chapter treats of the application of NHC-capped cyclodextrin-gold(I) complexes in catalysis.

Bibliographic Analysis

Chapter I - Application of Gold Catalysis to the Total Synthesis of Terpenoid Natural Products

The total synthesis of small-molecule natural products plays an important role in biomedical research. The transition-metal-catalyzed reactions have been frequently used for the key construction of chemical bonds in the synthesis of natural products. In its cationic form, gold has proven to catalyse many organic reactions, including new transformations. Hence, it has significantly enriched the arsenal of transformations available for total synthesis. The “soft” Lewis acidity of large cationic Au(I) ions, that share the positive charge with their ligand, results in a preference for them binding to “soft” Lewis bases such as the π -systems of alkenes and alkynes rather than oxygen. The resulting high air and moisture stability of gold catalysts adds to their practical value in terms of their application in organic synthesis. This combined with high gain in molecular complexity,⁸ exceptionally mild reaction conditions and high atom economy⁹ has resulted in a number of applications of the ability of homogeneous gold catalysis to construct complex ring systems in natural product synthesis.¹⁰ The following section focuses on the use of chemo- and regioselective gold(I)-catalyzed transformations in the total synthesis of complex terpenoid natural products, with the mode of activation of the substrate by the gold catalyst being discussed.

I. Gomerone C – Application of the Gold-Catalyzed Conia-Ene Reaction

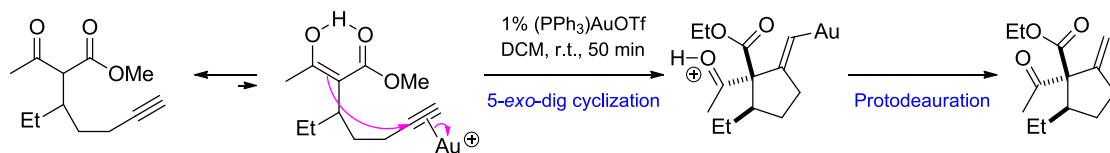
In 2004, Toste and co-workers reported the gold(I)-catalyzed cyclizations of enolizable β -ketoesters and β -diketones onto appended alkynes as a method for the formation of cyclopentenones. The proposed mechanism involves the addition of the enol tautomer of the ketoester to a gold(I)-complexed alkyne and subsequent protonolysis of the resulting vinyl-gold(I) species (*Scheme 1*).¹¹

⁸ Bertz, S.H. *J. Am. Chem. Soc.* **1981**, *103*, 3599. For reviews on molecular complexity, see: Fensterbank, L., Malacria, M. *Acc. Chem. Res.* **2014**, *47*, 953-915; Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208-3221; Echavarren, A.M., Jimenez-Nunez, E. *Top. Catal.* **2010**, *53*, 924-930.

⁹ Trost, B.M. *Science* **1991**, *254*, 1471; Trost, B.M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259.

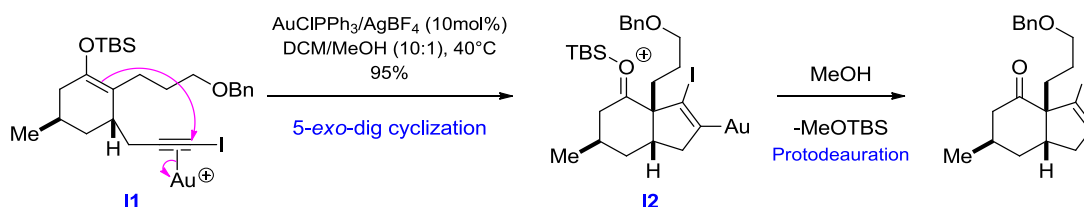
¹⁰ For reviews on the use of gold catalysis in total synthesis, see: Hashmi, A.S.K., Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766-1775; Rudolph, M., Hashmi, A.S.K. *Chem. Soc. Rev.* **2012**, *41*, 2448-2462; Zhang, Y., Luo, T., Yang, Z. *Nat. Prod. Rep.* **2014**, *31*, 489.

¹¹ Kennedy-Smith, J.J., Staben, S.T., Toste, F.D. *J. Am. Chem. Soc.* **2004**, *126*, 4526; Staben, S.T., Kennedy-Smith, J.J., Toste, F.D. *Angew. Chem. Int. Ed.* **2004**, *43*, 5350.



Scheme 1 Gold(I)-catalyzed Cyclization of β -ketoesters

The reaction allowed the diastereoselective formation of a variety of cyclic and bicyclic systems but the method is limited to the synthesis of quaternary carbon atoms that bear two carbonyl functionalities. To broaden the scope of the reaction, the gold(I)-catalyzed cyclization of silyl enol ethers onto alkynes was envisioned. However, silyl enol ethers lack the proton source necessary for the protonolysis of the vinyl gold intermediate, so that an external proton source is required to complete the catalytic cycle. In addition, the competitive reaction of this proton source and the electrophilic cationic gold(I) species with the highly nucleophilic silyl enol ether must be avoided. MeOH was found to fit these requirements. For instance, reaction of silyl enol ether **11** with a catalytic amount of $[\text{PPh}_3\text{AuCl}]/\text{AgBF}_4$ in a 10:1 dichloromethane/MeOH mixture at 40°C gave hydrindanone vinyl iodide **12** in 95% yield as a single diastereomer (*Scheme 2*). It is noteworthy that the identity of the counterion proved to be key as other complexes, such as ClO_4 , SbF_6 and OTf salts, produced varying amounts of hydrolysed enol ethers.¹² This methodology was successfully applied to the total syntheses of (+)-Lycoplidine A and (+)-Fawcettimine.¹³



Scheme 2 Gold(I)-catalyzed Cyclization of Silyl Enol Ethers

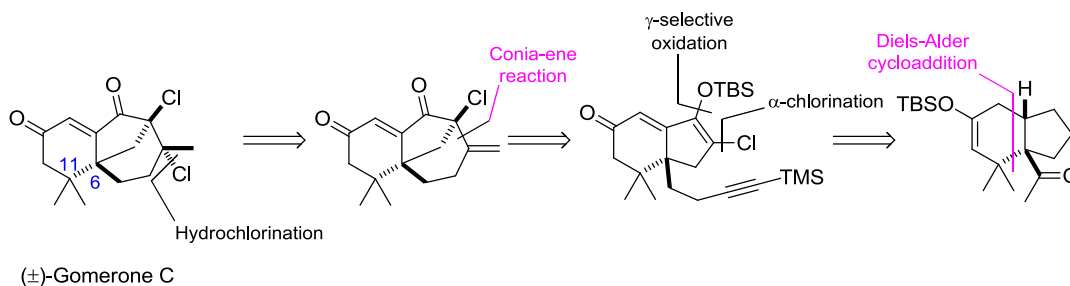
In 2012, Carreira *et al.* reported the first total synthesis of Gomerone C,¹⁴ a sesquiterpene isolated from the red alga *Laurencia majuscula*. For this purpose, they proposed a strategy based on the formation of the fused 5,6-membered ring system and the installation of the two quaternary centers at C6 and C11 *via* a Diels-Alder cycloaddition, and the late

¹² Staben, S.T., Kennedy-Smith, J.J., Huang, D., Corkey, B.K., LaLonde, R.L., Toste, F.D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991-5994.

¹³ Linghu, X., Kennedy-Smith, J.J., Toste, F.D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671-7673.

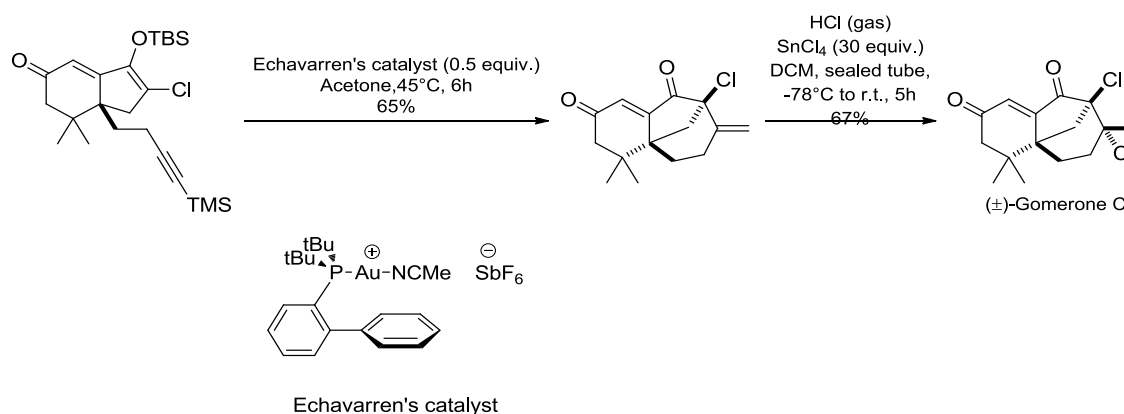
¹⁴ Huwyler, N., Carreira, E.M. *Angew. Chem. Int. Ed.* **2012**, *51*, 13066-13069.

construction of the angular tricyclic carbon skeleton *via* a Conia-ene reaction involving an α -chlorinated silyl enol ether and a silylated alkyne (*Scheme 3*).



Scheme 3 Retrosynthetic Analysis of Gomerone C

Treatment of the key Conia-ene precursor with Echavarren's catalyst in dry acetone at 45°C effected both the cyclization as well as the concomitant removal of the silyl protecting group on the alkyne,¹⁵ the mechanism of which is unclear. This was the first example of gold(I)-mediated Conia-ene reaction involving a chlorinated silyl enol ether. Then, the synthesis was achieved by hydrochlorination of the exocyclic double bond (*Scheme 4*).



Scheme 4 Key Gold(I)-mediated Conia-ene Cyclization and Completion of the Total Synthesis of (±)-Gomerone C

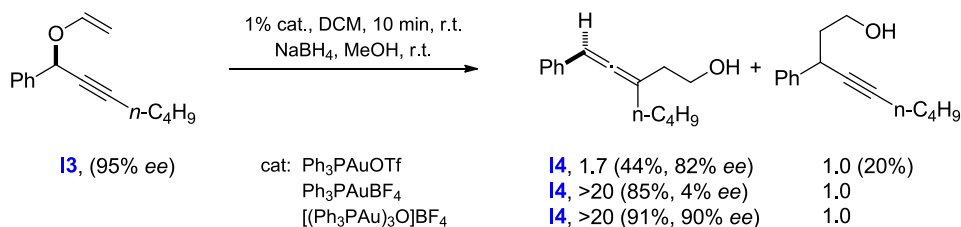
II. Azadirachtin A – Application of the Gold(I)-Catalyzed Claisen Rearrangement

In 2004, Toste and co-workers reported a gold(I)-catalyzed propargyl Claisen rearrangement.¹⁶ While Ph₃PAuOTf affords the desired allene along with a substantial amount of the product derived from the competing [1,3]-rearrangement, changing the counterion from

¹⁵ For examples of the removal of silyl protecting groups under gold catalysis, see: Barabé, F., Bétournay, G., Bellavance, G., Barriault, L. *Org. Lett.* **2009**, *11*, 4236-4238; Nieto-Oberhuber, C., Lopez, S., Echavarren, A.M. *J. Am. Chem. Soc.* **2005**, *127*, 6178-6179.

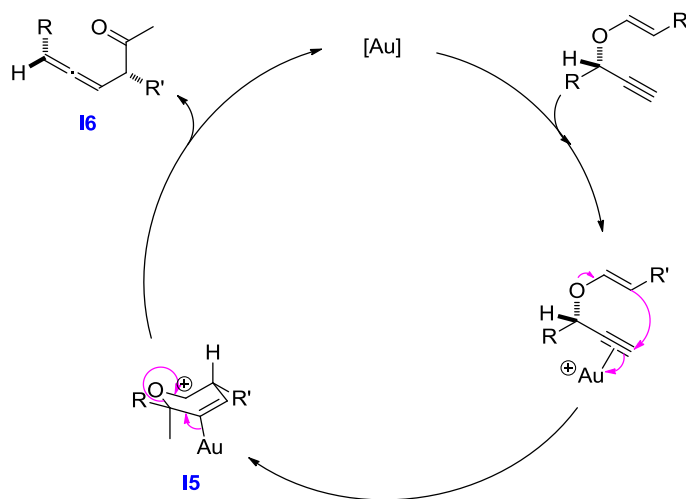
¹⁶ Sherry, B.D., Toste, F.D. *J. Am. Chem. Soc.* **2004**, *126*, 15978-15979.

triflate to tetrafluoroborate allows a complete regiocontrol. Yet, almost racemic homoallylic alcohol **14** is formed from propargyl vinyl ether **13**. However, treatment of enantioenriched propargyl vinyl ether **13** with 1 mol% [(Ph₃PAu)₃O]BF₄ afforded homoallylic alcohol **14** in 91% yield and with nearly complete chirality transfer (*Scheme 5*). The reaction was proved to be diastereoselective and its efficiency was illustrated by the ability to perform a number of reactions 0.1 mol% [(Ph₃PAu)₃O]BF₄.



Scheme 5 Gold(I)-catalyzed Propargyl Claisen Rearrangement

The proposed mechanism is based on a cyclization-induced rearrangement catalysed by Au(I).¹⁷ A 6-*endo*-dig addition of the enol ether onto the gold(I)-alkyne complex results in the formation of intermediate **15**. The diastereoselectivity of the rearrangement can be accounted for by considering the half-chair transition state¹⁸ leading to **16**. The vinyl substituent (R') occupies a pseudo equatorial position, and the propargylic group (R) adopts a pseudoaxial orientation in order to avoid A^{1,2}-strain with the vinyl gold substituent. Grob-type fragmentation of **15** affords the β-allenic aldehyde and regenerates the cationic Au(I) catalyst (*Scheme 6*).

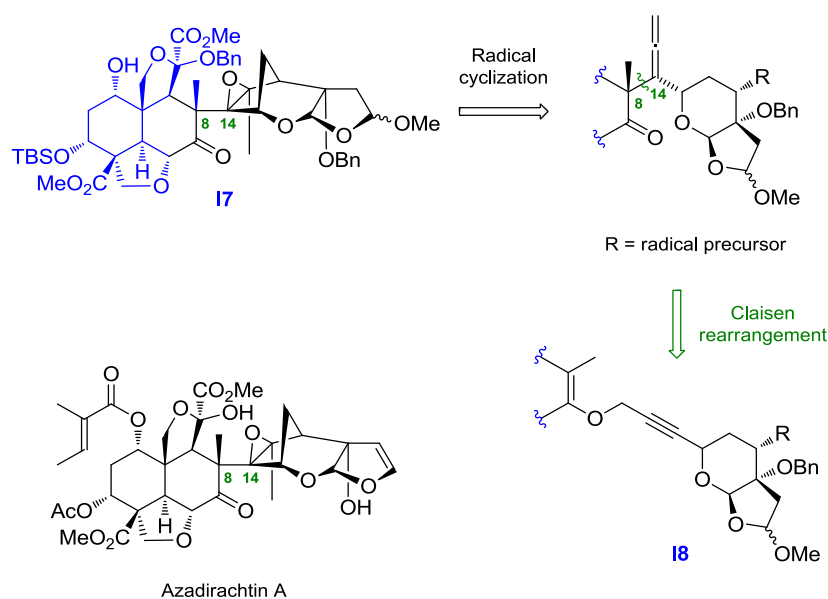


Scheme 6 Proposed Mechanism for the Gold(I)-catalyzed Propargyl Claisen Rearrangement

¹⁷ Overman, L.E. *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 579.

¹⁸ For a discussion on the transition state of the thermal propargyl Cope rearrangement, see: Owens, K.A., Berson, J.A. *J. Am. Chem. Soc.* **1990**, 112, 5973; Black, K.A., Wilsey, S., Houk, K.N. *J. Am. Chem. Soc.* **1998**, 120, 5622.

Azadirachtin A is a very complex natural product, isolated in 1968 from the Indian neem tree *Azadirachta indica* by Morgan and Butterworth.¹⁹ Although this compound has been the subject of a lot of synthetic studies, the only successful strategy toward its total synthesis has been reported to by Ley and co-workers,²⁰ and is based on a degradative approach from the target molecule **17**. In response to the failure of a number of strategies aimed at directly installing the C8–C14 linkage,²¹ Ley *et al.* developed a synthetic route that proceeded *via* the Claisen rearrangement of propargylic enol ether **18** (Scheme 7).



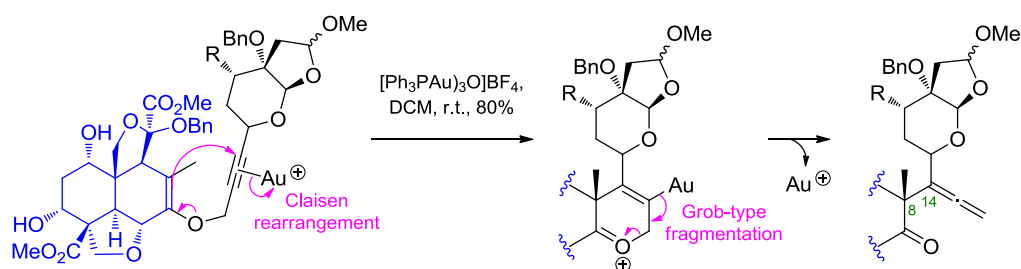
Scheme 7 Retrosynthetic Analysis of **17** Precursor to Azadirachtin A

The Claisen rearrangement necessitates microwave heating at 185°C to afford the allene but is successfully conducted at room temperature in the presence of $[(\text{Ph}_3\text{PAu})_3\text{O}]\text{BF}_4$. Such a strategy allows for the construction of the C8–C14 bond (Scheme 8). The synthesis of **17** was then completed in 5 steps. This was the first example of the application of the gold-catalyzed propargyl Claisen rearrangement to total synthesis.

¹⁹ Butterworth, J.H., Morgan, E.D. *Chem. Commun.* **1968**, 23-24.

²⁰ Veitch, G.E., Beckmann, E., Burke, B.J., Boyer, A., Maslen, S.L., Ley, S.V. *Angew. Chem. Int. Ed.* **2007**, 46, 7629-7632.

²¹ Ley, P.V. *Pure Appl. Chem.* **2005**, 77, 1115-1130; Anderson, J.C., Ley, S.V. *Tetrahedron Lett.* **1990**, 31, 431-432; Gutteridge, C.E., PhD Thesis, University of Cambridge, **1996**; Pape, A.R., PhD Thesis, University of Cambridge, **1999**.

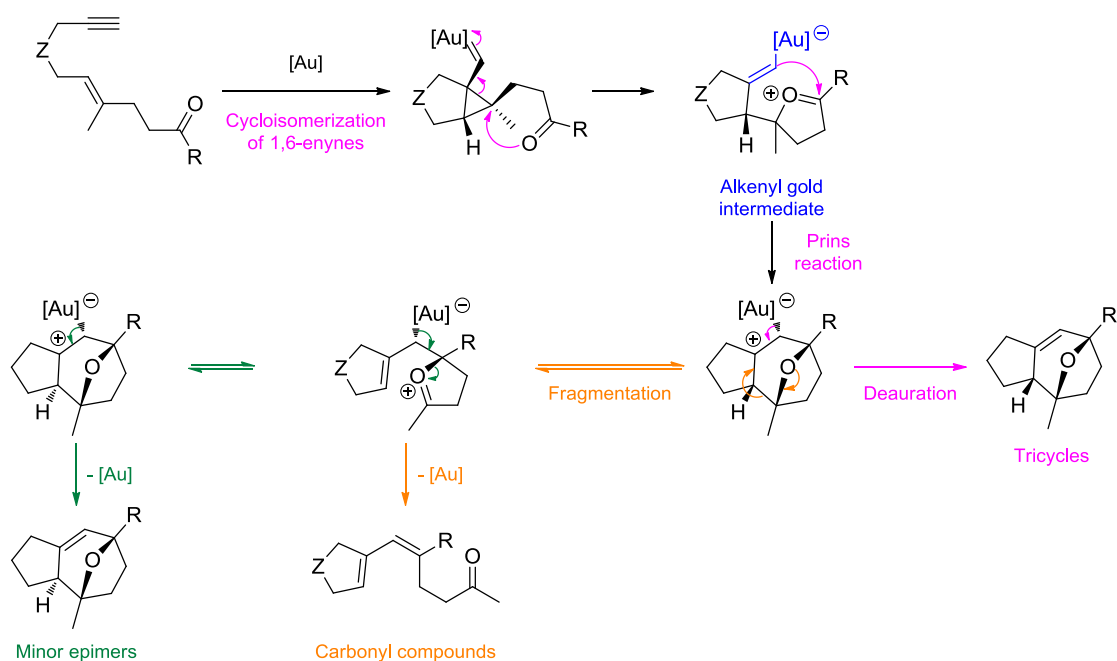


Scheme 8 Construction of the C8-C14 Linkage of Azadirachtin A via the Claisen Rearrangement of Propargylic Enol Ether 18

III. Pubinernoid B, Orientalol F and Englerin A

In 2006, Echavarren *et al.* reported the possibility of Prins intramolecular cyclizations in the Au-catalyzed reactions of 1,6-enynes, thus allowing the one-step synthesis of tricyclic skeletons (Scheme 9).²² Specifically, enynes bearing a carbonyl group at the alkenyl side chain were cyclized to give oxatricyclic derivatives by using Au^I catalysts. The carbonyl group acts as an internal nucleophile. An oxonium cation is formed, onto which the alkenyl gold intermediate adds (Prins reaction). Then, deauration leads to tricycles (Scheme 9, Pink arrow), whereas fragmentation of the seven-membered ring affords carbonyl compounds (Scheme 9, Orange arrow). This formal [2+2+2] alkyne/alkene/carbonyl cycloaddition of ketoenynes is stereoselective. Minor epimers are formed *via* competitive 2-oxonia-Cope rearrangement (Scheme 9, Green arrow).

²² Jimenez-Nunez, E., Claverie, C.K., Nieto-Oberhuber, C., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5452-5455.



Scheme 9 Prins Cyclization in the Gold-catalyzed Reaction of Enynes

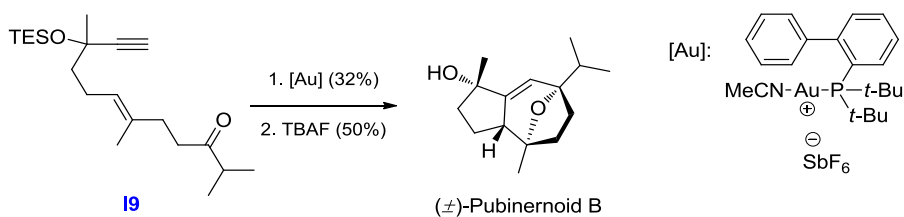
This process has been applied to propargyl alcohols toward the total syntheses of (\pm)-Pubinernoid B,²³ (+)-Orientalol F²⁴ and (-)-Englerin A²⁵. Propargylic alcohols are prone to undergo Meyer Schuster rearrangement or nucleophilic attack under gold-catalysis. As for propargylic carboxylates, they readily undergo gold-catalyzed 1,2- or 1,3-acyl migrations. In addition, propargyl alcohols, ethers and silyl ethers undergo gold(I)-catalyzed intramolecular 1,5-migration of OR groups. A faster attack of the carbonyl group than the migration of the OR group was thus required to achieve selectivity and represented one major challenge of the syntheses.

Regarding (\pm)-Pubinernoid B, the best yields of the cyclized products were obtained with the TES protecting group (Scheme 10). AuCl was inefficient. However, cationic gold complexes afforded the expected oxatricyclic product as a single stereoisomer. Worthy of note, the use of silver-free catalysts was crucial for consistent yields of the desired product to be obtained, indicating that Ag^I may not be innocent in these cyclizations. Pubinernoid B was formed in a modest 16% yield over two steps from substrate **19** in the presence of Echavarren's catalyst followed by desilylation of the major cyclization product with TBAF (Scheme 10).

²³ Huang, S.-X., Yang, J., Xiao, W.-L., Zhu, Y.-L., Li, R.-T., Li, L.-M., Pu, J.-X., Li, X., Li, S.-H., Sun, H.-D. *Helv. Chim. Acta* **2006**, *89*, 1169-1175; Jimenez-Nunez, E., Molawi, K., Echavarren, A.M. *Chem. Commun.* **2009**, 7327-7329.

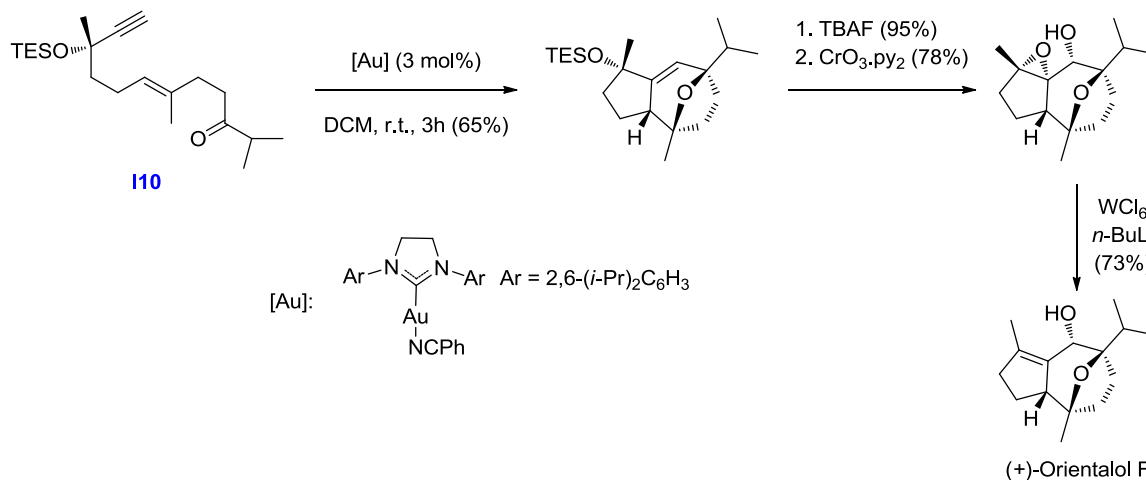
²⁴ Peng, G.-P., Tian, G., Huang, X.-F., Lou, F.-C. *Phytochemistry* **2003**, *63*, 877-881; Jimenez-Nunez, E., Molawi, K., Echavarren, A.M. *Chem. Commun.* **2009**, 7327-7329.

²⁵ Ratnayake, R., Covell, D., Ransom, T.T., Gustafson, K.R., Beutler, J.A. *Org. Lett.* **2003**, *11*, 56-60.



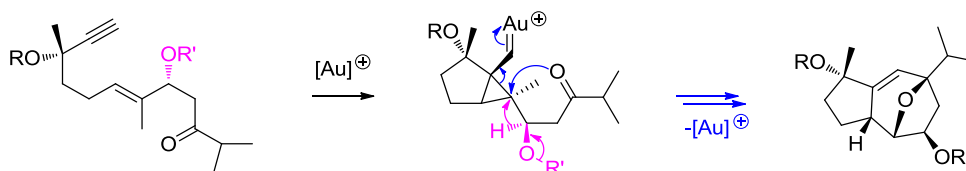
Scheme 10 Application of the [2+2+2] alkyne/alkene/carbonyl Cycloaddition Process to the Total Synthesis of (±)-Pubinernoid B

The synthesis of (+)-Orientalol F necessitated the more sophisticated substrate **110**, the gold-cyclization of which afforded the expected polycyclic compound in 65% yield. (+)-Orientalol F was then completed in 3 steps (Scheme 11).



Scheme 11 Application of the [2+2+2] alkyne/alkene/carbonyl Cycloaddition Process to the Total Synthesis of (+)-Orientalol F

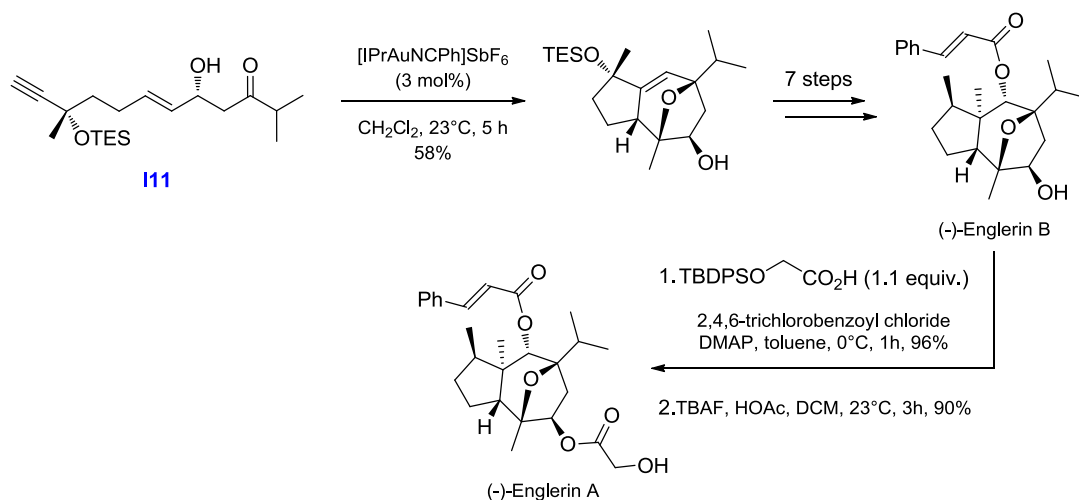
The guaiane sesquiterpene (-)-Englerin A has been shown to be 1-2 orders of magnitude more potent than taxol against cancer cell lines, whereas (-)-Englerin B was much less active and selective. As compared to the total syntheses of (±)-Pubinernoid B and (+)-Orientalol F, the additional allylic OR' group could interfere in the presence of Lewis acidic gold(I) catalysis. Especially, the OR' group might compete the carbonyl group in the opening of the gold carbenoid intermediate (Scheme 13, pink arrows).



Scheme 13 Competitive Opening of the Gold Carbenoid Intermediate in the Presence of an Additional Allylic OR' Group

Nevertheless, the reaction proceeds stereoselectively when a highly donating ligand is used, with both allylic and propargylic substituents (OR or OR', respectively) being tolerated

(Scheme 13). The best results were obtained by using the unprotected aldol substrate **111** with [IPrAuNCPPh]SbF₆ (3 mol%) as the catalyst. The expected oxatricyclic product was obtained in 58% yield as a single diastereomer. Under these conditions, the reaction could be performed on gram-scale. Other catalysts, however, gave poor results. Both (-)-Englerin B and A were then obtained in 7 and 9 steps respectively (Scheme 13).

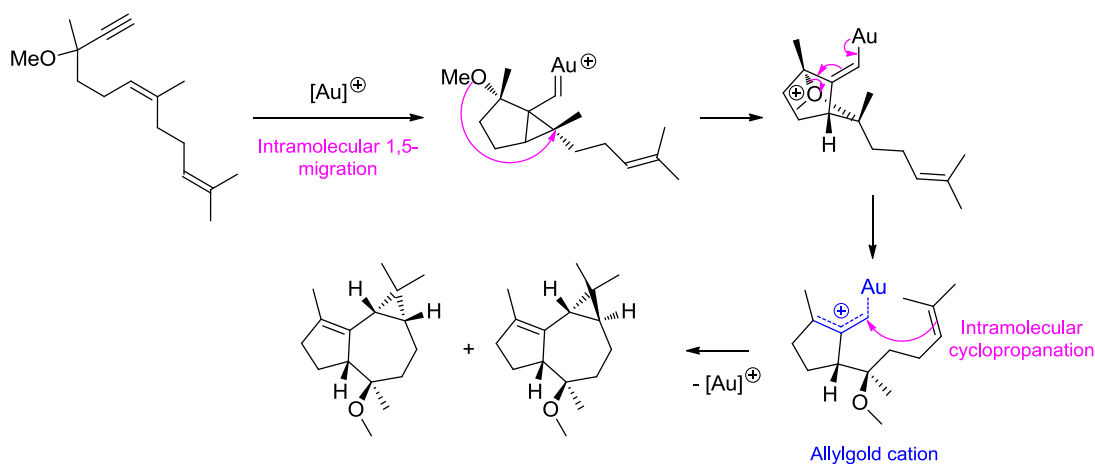


Scheme 13 Application of the [2+2+2] alkyne/alkene/carbonyl Cycloaddition Process to the Total Synthesis of (-)-Englerin B and A

IV. (+)-Schisanwilsonene A

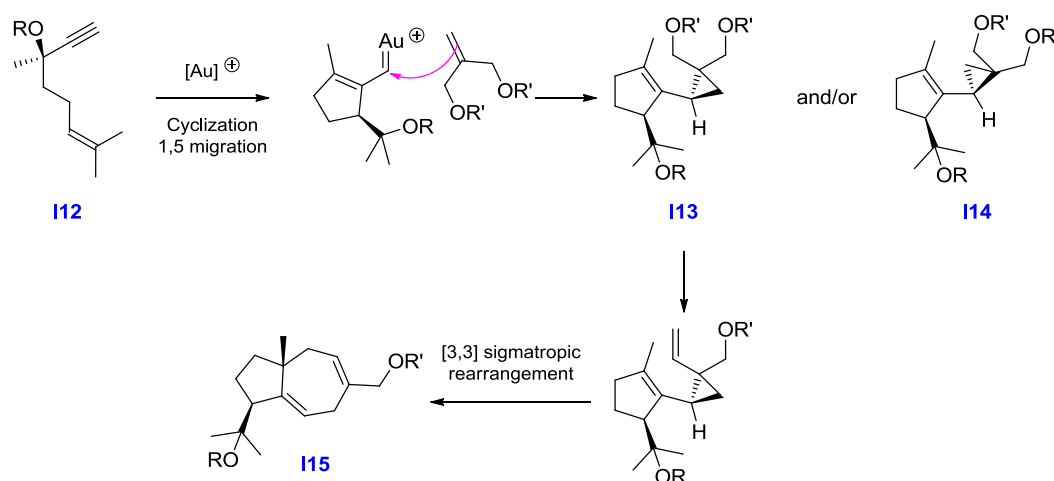
In 2009, Echavarren *et al.* reported that under gold catalysis, propargyl alcohols, ethers and silyl ethers undergo intramolecular 1,5-migration.²⁶ Upon activation of the alkyne, a gold carbenoid intermediate is formed. Then, intramolecular 1,5-migration of the OR group and concomitant opening of the cyclopropane leads to an allylgold cation. Tricyclic compounds are obtained *via* the intramolecular cyclopropanation of the pendant alkene (Scheme 14).

²⁶ Jimenez-Nunez, E., Raducan, M., Lauterbach, T., Molawi, K., Solorio, C.R., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6152-6155.



Scheme 14 Intramolecular 1,5-Migration of Propargyl Ethers

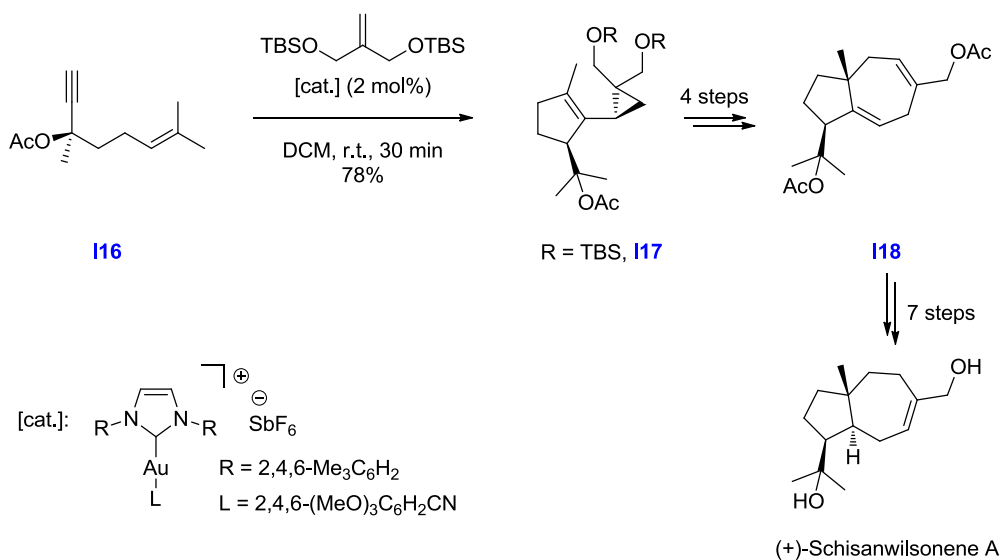
(+)-Schisanwilsonene A is a carotene-type sesquiterpenoid, which was isolated from a medicinal plant indigenous to southern China and exhibits antiviral activity. The first total synthesis of Schisanwilsonene A was reported by Echavarren *et al.*, with a strategy based on their previously reported tandem reaction of 1,6-enynes substituted with propargylic alkoxy groups.²⁷ Thus, they envisioned the possibility that propargylic alcohol **112** may react under gold catalysis to form the α,β -unsaturated gold carbene (*Scheme 15*). Intermolecular cyclopropanation affords products **113** and **114**. Then, hexahydroazulene **115** is obtained after selective methylenation of one of the diastereotopic alkoxymethylene groups and [3,3] sigmatropic rearrangement. The orientation of the external alkene is crucial, since **114** would not lead to the expected hexahydroazulene core.



Scheme 15 Synthetic Strategy toward the Total Synthesis of (+)-Schisanwilsonene A

²⁷ Gaydou, M., Miller, R.E., Delpont, N., Ceccon, J., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2013**, 52, 6396-6399.

(+)-Schisanwilsonene A was synthesized starting from propargyl acetate **I16** (Scheme 16). Interestingly, the expected product **I17** was obtained as a single diastereomer, though propargyl acetates tend to react with gold catalysts by 1,2- or 1,3-acetate migration. The bicyclic diene **I18** was prepared in four steps *via* selective methylenation and [3,3] sigmatropic rearrangement. Then, seven more steps were required to complete the synthesis of (+)-Schisanwilsonene A.



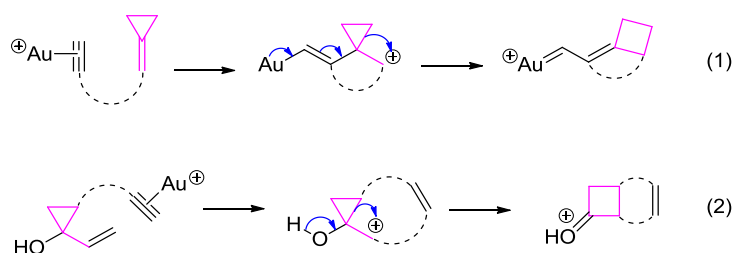
Scheme 16 Key Gold-Catalyzed Transformation in the Total Synthesis of (+)-Schisanwilsonene A

V. Ventricosene

In 2008, the group of Toste reported a cycloisomerization/ring expansion tandem reaction involving enynes containing an embedded cyclopropane unit.²⁸ Ring systems containing a cyclopropylmethyl cation are selectively formed, which undergo Wagner-Merwein shift to provide diastereomerically pure fused cyclobutanes.

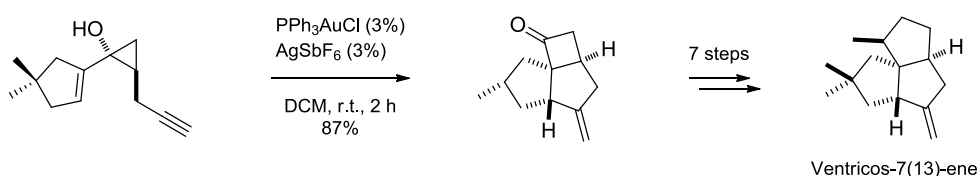
Both alkylidenecyclopropanes and vinylcyclopropanes can actually be used as precursors to the cyclopropylmethyl cation. In the case of alkylidenecyclopropanes, electron donation from gold may help the σ -bond migration (Scheme 17, equation (1)). Regarding vinylcyclopropanols, a semipinacol rearrangement leads to cyclobutanone products (Scheme 17, equation (2)). Of note, *cis*-disubstituted cyclopropanol substrates are necessary to maintain proximity between insaturations involved in the cycloisomerization process. A high stereoselectivity was observed for the cycloisomerization of cyclic olefins.

²⁸ Sethofer, S.G., Staben, S.T., Hung, O.Y., Toste, F.D. *Org. Lett.* **2008**, *10*, 4315-4318.



Scheme 17 Cycloisomerization/Ring Expansion Tandem Reaction of Enynes

The tandem cyclization/semipinacol rearrangement was further applied to the total synthesis of the angular triquinane ventricos-7(13)-ene (*Scheme 18*). The gold(I)-catalyzed reaction proceeded smoothly at r.t. and the expected cyclobutanone was obtained in 87% yield as a single diastereomer. The total synthesis of Ventricos-7(13)-ene was then completed in 7 steps.



Scheme 18 Application of the Tandem Cyclization/Semipinacol Rearrangement to the Total Synthesis of Ventricos-7(13)-ene

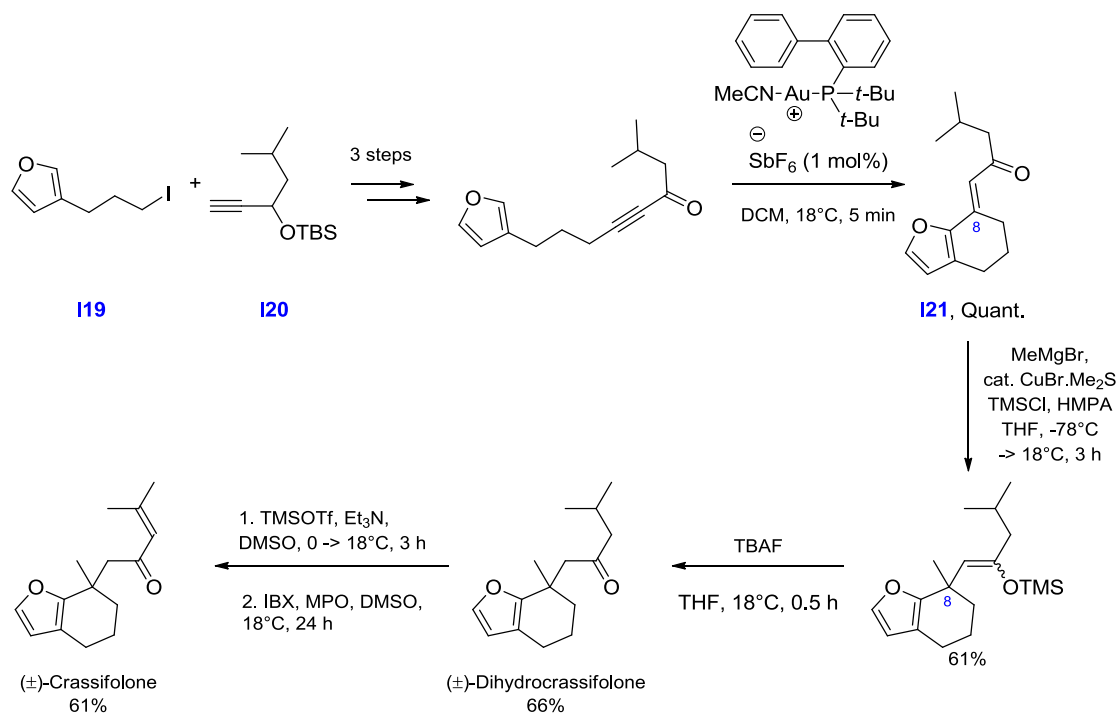
VI. (\pm)-Crassifolone and (\pm)-Dihydrocrassifolone – Application of the Gold(I)-Catalyzed Michael Reaction

(\pm)-Crassifolone and (\pm)-Dihydrocrassifolone were found in essential oils derived from the wood of *Myoporum crassifolium*, a tree growing in Noumea (New Caledonia). Though their structures have been established through ^1H and ^{13}C NMR experiments, their absolute configurations remain undefined. No significant biological activity was ascribed to these natural products, which may be used as fragrances.²⁹ The total syntheses of the above-mentioned natural products were envisioned *via* an unprecedented Au(I)-catalyzed intramolecular nucleophilic addition of a furan moiety onto a Michael acceptor (*Scheme 19*).³⁰ The substrate required for the intramolecular Michael addition reaction was prepared in three steps from building blocks **119** and **120**. Reaction of this starting material with 1 mol% of Echavarren's Au(I) catalyst in dichloromethane at 18°C for 5 minutes afforded isomer **121** in quantitative yield.

²⁹ Menut, C., Cabalion, P., Hnawia, E., Agnani, H., Waikedre, J., Fruchier, A. *Flavour Fragrance J.* **2005**, *20*, 621.

³⁰ Addition of the nucleophilic pyrrole moiety to a Michael acceptor had previously been reported in the literature: Banwell, M.G., Beck, D.A.S., Smith, J.A. *Org. Biomol. Chem.* **2004**, *2*, 157; Banwell, M.G., Beck, D.A.S., Willis, A.C. *ARKIVOC* **2006**, *iii*, 163.

Then, treatment with excess methylmagnesium bromide in the presence of a catalytic amount of a copper(I) salt and a stoichiometric amount of TMSCl allowed the construction of the quaternary centre in position 8. The ketone-conjugated carbon-carbon double bond present in Crassifolone was formed according to a protocol defined by Lalic and Corey,³¹ which consists in treatment with TMSOTf and Et₃N, then with IBX in the presence of MPO (4-methoxypyridine N-oxide).³²



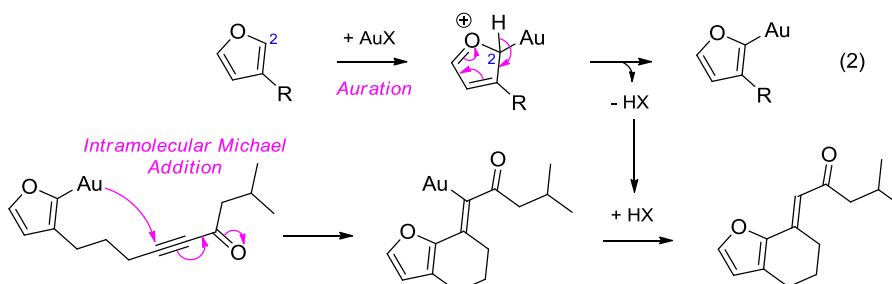
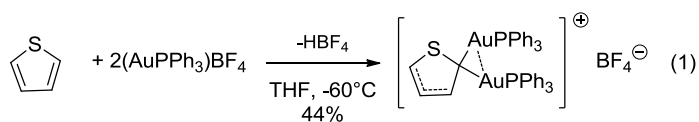
Scheme 19 Total Syntheses of (±)-Crassifolone and (±)-Dihydrocrassifolone

In 2003, Schmidbaur reported that the treatment of thiophene with (PPh₃Au)BF₄ in THF at low temperature affords the diaurated thiophene complex in 44% yield (*Scheme 20*, equation (1)).³³ Accordingly, the authors envisioned auration at C2 of the furan moiety followed by intramolecular Michael addition as the mechanism (*Scheme 20*, equation (2)).

³¹ Lalic, G., Corey, E.J. *Org. Lett.* **2007**, 9, 4921. For a related example of the application of this dehydrogenation protocol, see: Austin, K.A.B., Banwell, M.G., Willis, A.C. *Org. Lett.* **2008**, 10, 4465.

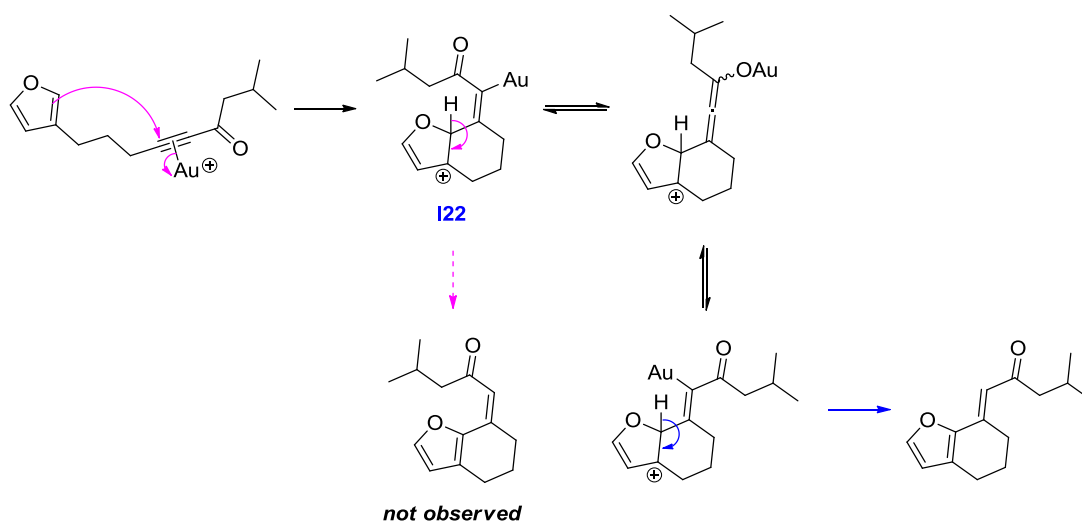
³² Nicolaou, K.C., Montagnon, T., Baran, P.S. *Angew. Chem. Int. Ed.* **2002**, 41, 993.

³³ Porter, K.A., Schier, A., Schmidbaur, H. *Organometallics* **2003**, 22, 4922-4927.



Scheme 20 Proposed Mechanism for the Intramolecular Michael Addition Reaction

The authors also mentioned the possibility of a Au(I)-catalyzed intramolecular hydroarylation reaction. However, in the latter mechanism, the *trans* addition of the furan moiety onto the enone would imply the formation of intermediate **122**, the isomerization of which through the allene species would be required for the formation of the observed isomer. Thus, it is likely that a mixture of isomers would be obtained in this case (*Scheme 21*).



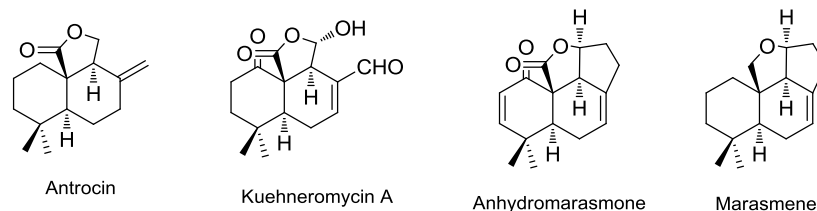
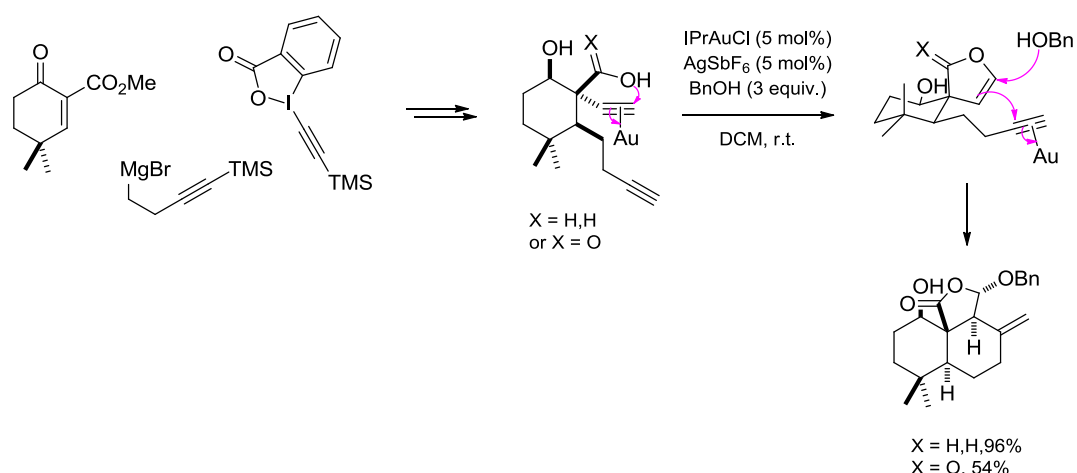
Scheme 21 Intramolecular Hydroarylation Mechanism

VII. Drimane-Type Sesquiterpenoids – Application of the Gold(I)-Catalyzed Diyne Tandem Reaction

Drimane-type sesquiterpenoids represent a large group of natural products with interesting biological activities.³⁴ Many of them are constructed on a tricyclic core structure

³⁴ Jansen, B.J.M., de Groot, A. *Nat. Prod. Rep.* **1991**, 8, 309-308; Jansen, B.J.M., de Groot, A. *Nat. Prod. Rep.* **2004**, 21, 449-477.

(Scheme 22, bottom part), which used to be synthesized by intramolecular Diels-Alder cycloaddition.³⁵ Yang *et al.* discovered that a key intermediate could be formed *via* the gold-catalyzed tandem reaction of a 1,7-enyne.³⁶ The precursor for the gold-catalyzed cascade reactions was prepared in 5 steps from readily available starting materials. The gold-catalyzed tandem reaction was then performed in the presence of IPrAuCl and AgSbF₆ (5 mol%). The 5-*endo*-dig addition of an internal oxygen nucleophile to one alkyne leads to a polarized olefin functionality, which functions as the nucleophile in the following 6-*exo*-dig cyclization, the reaction then being terminated by the nucleophilic addition of an external alcohol nucleophile, to give the expected tricyclic product as a single diastereomer (Scheme 22, upper part). Noteworthy, decreased yields were obtained when less electron-donating ligands were used. Exploration of the scope of the reaction revealed the importance of the cycloalkane scaffold as well as the *trans* relationship between the two alkynes for the second cyclization. The gold-catalyzed tandem reaction was then applied to the total syntheses of Kuehneromycin A, Antrocin, Anhydromarasmone and Marasmene (Scheme 22, bottom part). The targeted natural products were obtained from these intermediates following functional group manipulations.



Scheme 22 Gold-catalyzed Tandem Reaction in the Total Syntheses of Drimane-type Sesquiterpenoids

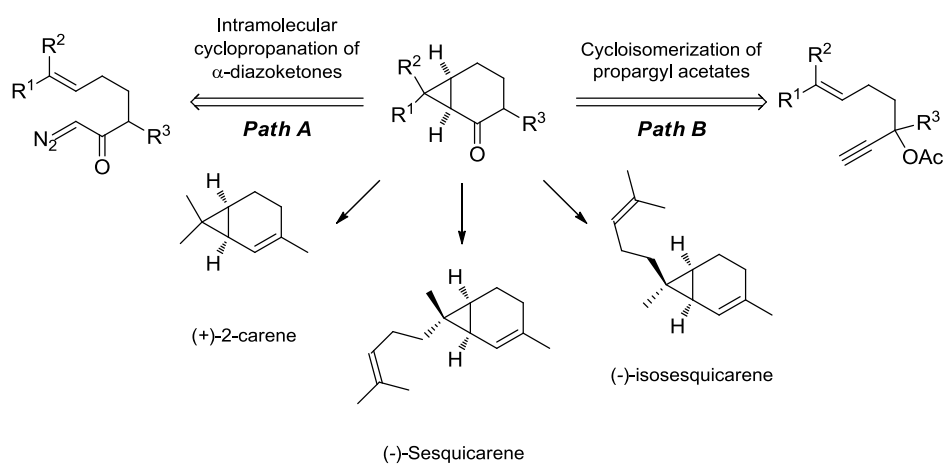
³⁵ Jauch, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2764–2765; Suzuki, Y., Nishimaki, R., Ishikawa, M., Murata, T., Takao, K.-i., Tadano, K.-i. *J. Org. Chem.* **2000**, *65*, 8595–8607; Suzuki, Y., Ohara, A., Sugaya, K., Takao, K.-i., Tadano, K.-i. *Tetrahedron* **2001**, *57*, 7291–7301; Jauch, J. *Eur. J. Org. Chem.* **2001**, 473–476; Jauch, J. *Synlett* **2001**, 87–89; Jauch, J., Wallner, C., Herdtweck, E. *Eur. J. Org. Chem.* **2003**, 3060–3064; Ishihara, J., Yamamoto, Y., Kanoh, N., Murai, A. *Tetrahedron Lett.* **1999**, *40*, 4387–4390.

³⁶ Shi, H., Fang, L., Tan, C., Shi, L., Zhang, W., Li, C., Luo, T., Yang, Z. *J. Am. Chem. Soc.* **2011**, *133*, 14944–14947.

VIII. Application of the Metal-Catalyzed Propargyl Ester Migrations

1. 2-sesquicarene, 2-carene and Episesquicarene

Fürstner *et al.* made use of the metal-catalyzed cycloisomerization reaction of propargyl acetates (Scheme 23, Path A) to replace the intramolecular cyclopropanation of unsaturated α -diazoketones³⁷ (Scheme 23, Path B) used so far in the synthesis of the cyclopropyl carbonyl derivative precursor to several terpenoids of the carene family,³⁸ for instance (+)-2-carene and its isoprenoid homologues (-)-2-sesquicarene and (-)-isosesquicarene.³⁹



Scheme 23 Preparation of Cyclopropyl Ketones from α -diazoketones (Path A) or by Metal-catalyzed Rearrangement of Propargyl Acetates (Path B)

The complexation of alkynes to gold makes them susceptible to the addition of nucleophiles such as alkenes, arenes, ethers or carbonyl groups.⁴⁰ Especially, anchimeric assistance from a propargyl acetate unit may lead to the formation of a gold carbenoid via 1,2-migration (Scheme 24, 1,2-migration), which can be trapped by a suitable alkene to form bicyclic

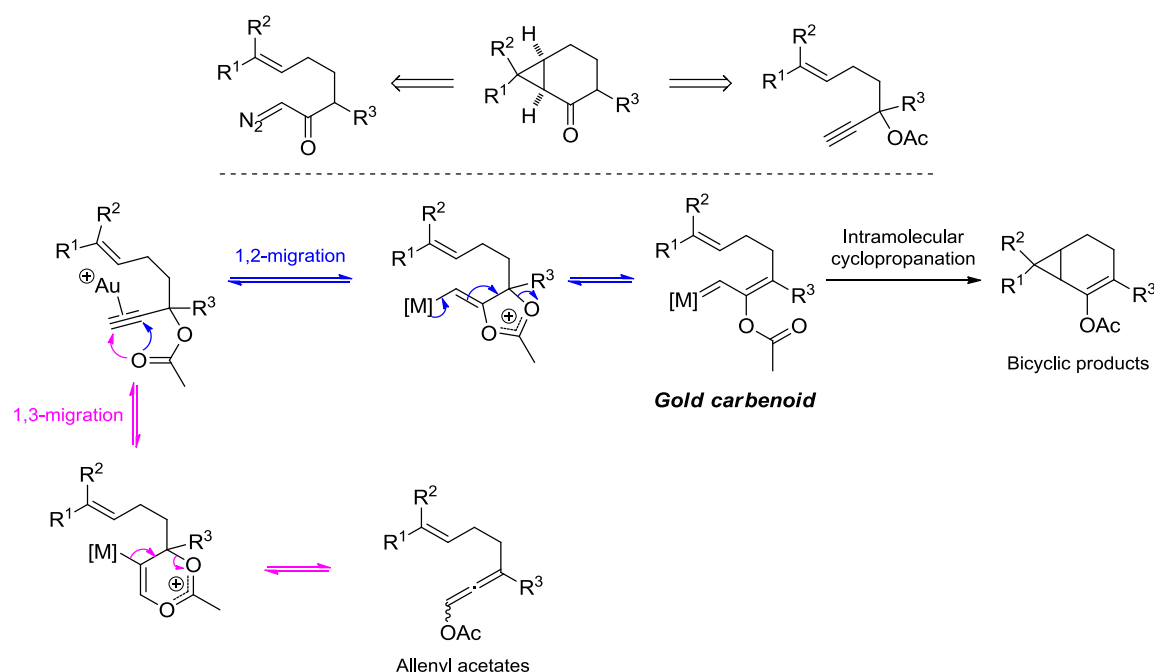
³⁷ α -Diazoketone cyclizations were pioneered by: Stork, G., Ficini, J. *J. Am. Chem. Soc.* **1961**, *83*, 4678. Reviews: Doyle, M.P., McKervy, M.A., Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds* **1998**, Wiley, New York; Davies, H.M.L., in *Comprehensive Organic Synthesis* **1991**, Trost, B.M., Fleming, I., eds., Pergamon, Oxford, *4*, 1031; Padwa, A., Krumpke, K.E. *Tetrahedron* **1992**, *48*, 5385.

³⁸ Fürstner, A., Hannen, P. *Chem. Commun.* **2004**, 2546-2547.

³⁹ Breitmaier, E. *Terpene. Aromen, Düfte, Pharmaka, Pheromone* **1998**, Teubner, Leipzig.

⁴⁰ Reviews: Mendez, M., Echavarren, A.M. *Eur. J. Org. Chem.* **2002**, 15; Lloyd-Jones, G.C. *Org. Biomol. Chem.* **2003**, *1*, 215; Aubert, C., Buisine, O., Malacria, M. *Chem. Rev.* **2002**, *102*, 813; Mendez, M., Mamane, V., Fürstner, A. *Chemtracts* **2003**, *16*, 397.

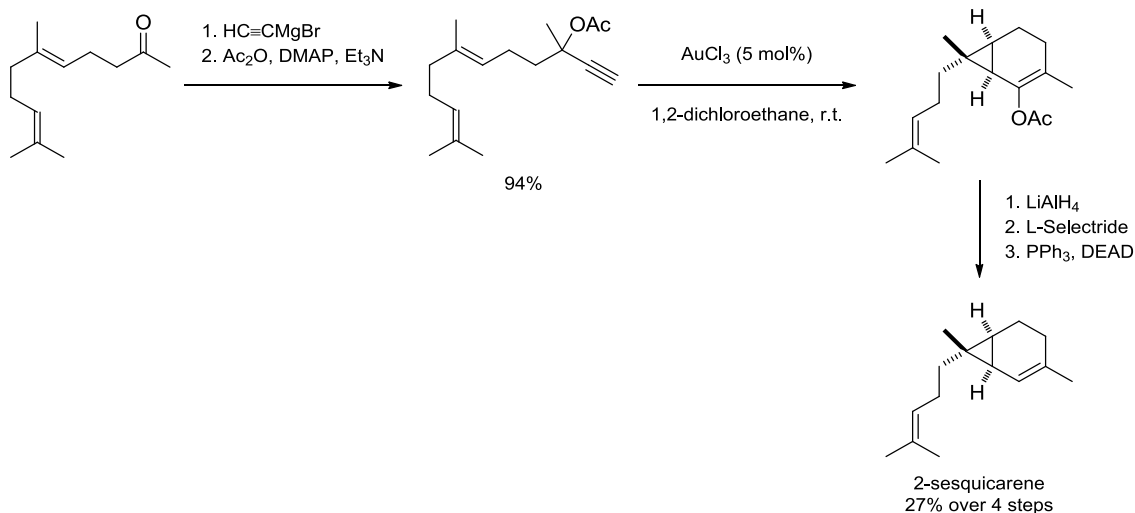
products.⁴¹ Hydrolysis of the resulting enol acetate leads to the expected carbonyl derivative. Alternatively, 1,3-migration of the propargyl acetate moiety leads to the reversible formation of allenyl acetates (*Scheme 24, 1,3-migration*).



Scheme 24 Simplified Mechanism for the Formation of Bicyclic Compounds from Propargyl Acetates

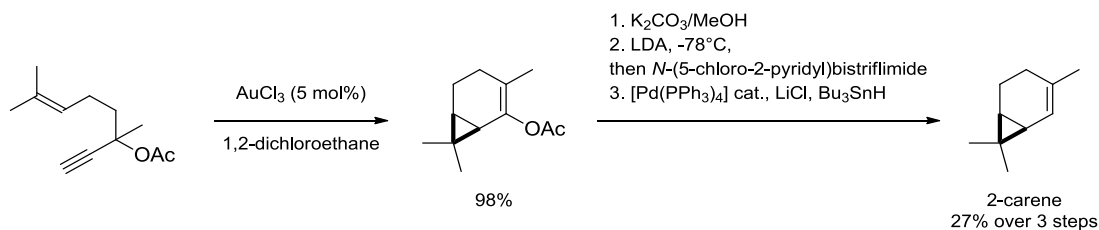
This concept was illustrated in the total synthesis of (\pm)-2-sesquicarene. For this purpose, geranylacetone was converted into the corresponding propargyl acetate in 94% yield over two steps. The desired bicyclo[4.1.0] skeleton was then formed in 95% yield in the presence of 5 mol% of AuCl₃, with marginal amount of allenyl acetate. As compared to the gold-catalyzed reaction, a significant amount of the allenyl acetate was formed under platinum catalysis. The total synthesis was completed by reductive cleavage of the ester with LiAlH₄, reduction of the resulting ketone in the presence of L-Selectride to afford the corresponding alcohol, and finally elimination in the presence of PPh₃ and DEAD (*Scheme 25*).

⁴¹ Mainetti, E., Mouriès, V., Fensterbank, L., Malacria, M. Marco-Contelles, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 2132; Harrack, Y., Blaszykowski, C., Bernard, M., Cariou, K., Mainetti, E., Mouriès, V., Dhimane, A.-L., Fensterbank, L., Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656; Miki, K., Ohe, K., Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505.



Scheme 25 Total Synthesis of (±)-2-sesquicarene

Similarly, carenyl acetate was isolated in 98% yield in the presence of AuCl₃. (±)-2-carene was then obtained *via* a sequence almost identical to that furnishing 2-sesquicarene (Scheme 26).



Scheme 26 Total Synthesis of (±)-2-carene

2. Cubebene and Cubebol

The first total synthesis of (-)-Cubebol,⁴² a tertiary alcohol featuring a highly condensed tricyclo[4.4.0.0]decane skeleton, was reported by Yoshikoshi and co-workers.⁴³ Their strategy was based on the cyclopropanation of a diazoketone. This route, however, was not diastereoface-selective and unfortunately, the desired ketone was obtained as the minor isomer in moderate yield. Therefore, Fürstner⁴⁴ and Fehr⁴⁵ independently envisioned the metal-catalyzed cycloisomerization of enynol esters as a more direct and efficient access to (-)-Cubebol.

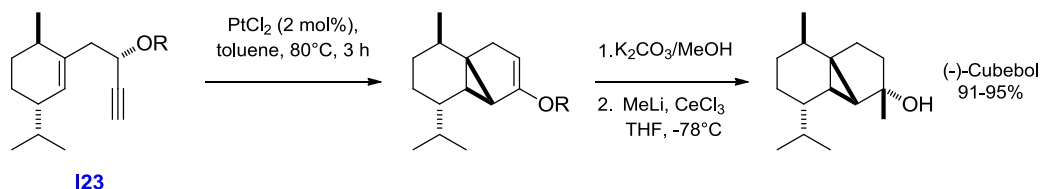
⁴² Vanasek, F., Herout, V., Sorm, F. *Collect. Czech. Chem. Commun.* **1960**, *56*, 919; Ohta, Y., Ohara, K., Hirose, Y. *Tetrahedron Lett.* **1968**, *9*, 4181, and references therein.

⁴³ Tanaka, A., Tanaka, R., Uda, H., Yoshikoshi, A. *J. Chem. Soc. Perkin 1* **1972**, 1721; Tanaka, A., Uda, H., Yoshikoshi, A. *Chem. Commun.* **1969**, 308. See also: Torii, S., Okamoto, T. *Bll. Chem. Soc. Jpn.* **1976**, *49*, 771.

⁴⁴ Fürstner, A., Hannen, P. *Chem. Eur. J.* **2006**, *12*, 3006-3019.

⁴⁵ Fehr, C., Galindo, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2901-2904.

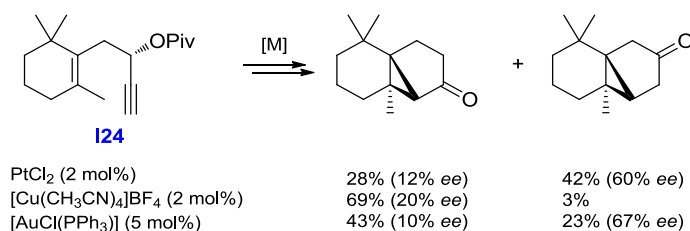
Indeed, propargyl acetate **123** reacted under platinum(II) catalysis to afford the expected tricyclic enol ester with excellent yield and diastereomeric ratio (*Scheme 27*). (-)-Cubebol was obtained after hydrolysis of the enol ester with $K_2CO_3/MeOH$ and diastereoselective addition of $MeLi/CeCl_3$.⁴⁶



Scheme 27 Total Synthesis of (-)-Cubebol

Fürstner and Fehr both made the observation that diastereomeric propargyl acetates react with different diastereoselectivities. The difference between the cycloisomerization of diastereomers of the same substrate indicates that the configuration of the stereogenic centre carrying the ester translates into the stereochemistry of the product. This position is therefore not planarized before cyclopropanation. Indeed, the formation of a vinyl carbenoid intermediate prior to cyclization implies that diastereomers of the same substrate lead to the same product distribution.

An additional reaction was run by Fehr and co-workers in order to examine the chirality transfer from the enantioenriched propargyl pivalate **124** (69% *ee*) (*Scheme 28*). The expected rearranged enol pivalate was obtained along with the isomeric non-rearranged enol pivalate. The enantiomeric excesses of these compounds were evidenced by those of their corresponding ketone derivatives (10-20% *ee* and 60-67% *ee* respectively).

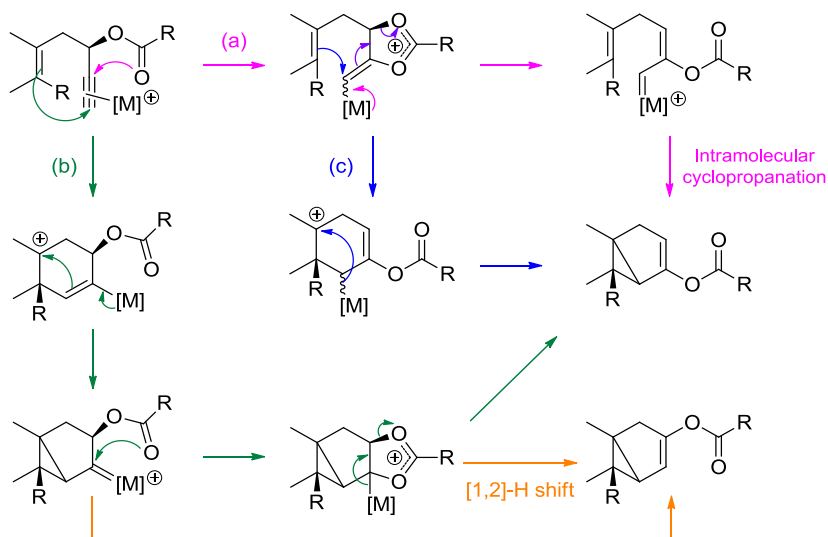


Scheme 28 Chirality Transfer in the Metal-catalyzed Rearrangement of Propargyl Esters

Cyclopropanation of the electron-rich olefin with the metal-complexed acetylene, followed by [1,2]-O-migration (*Scheme 29, path (b)*) would account for difference between the cycloisomerization of diastereomers of the same substrate but the presumed reaction course for the formation of the non-rearranged enol pivalate (*scheme 29, [1,2]-H shift*) does not explain why rearranged and non-rearranged cycloisomerization products exhibit different enantiomeric

⁴⁶ For a synthesis of racemic cubebenes, see: Piers, E., Britton, R.W., de Waal, W. *Tetrahedron Lett.* **1969**, 10, 1251; Piers, E., Britton, R.W., de Waal, W. *Can. J. Chem.* **1971**, 49, 12.

excess values. Hence, a third pathway was proposed for the cycloisomerization followed by [1,2]-acyl shift, involving the intramolecular addition of the ester carbonyl to the metal-complexed acetylene, thus affording a vinyl metal species, followed by nucleophilic addition of the double bond onto the oxy-allyl system and finally cyclopropane ring closure (*Scheme 29*, path (c)).



Scheme 29 Proposed Mechanism for the Metal-catalyzed Rearrangement of Propargyl Esters

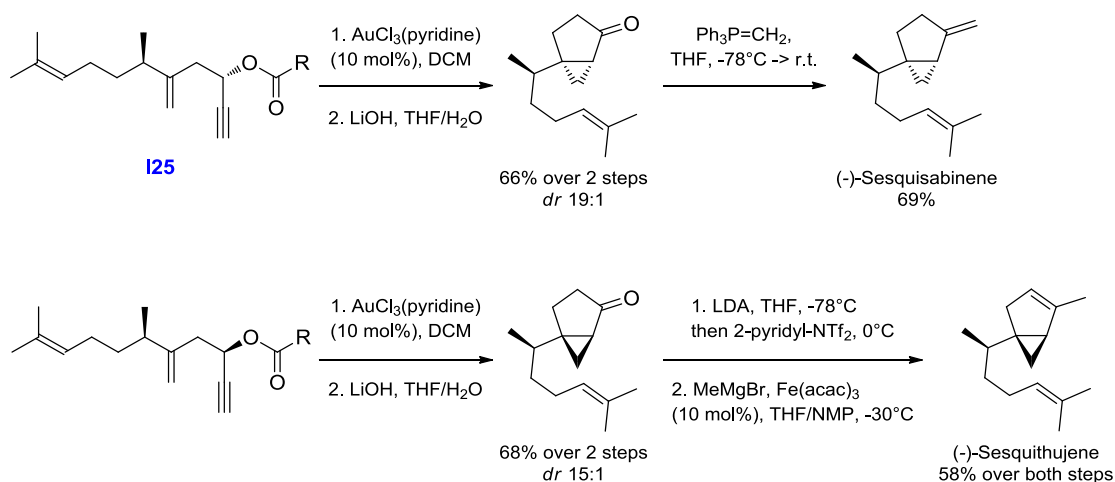
3. Sesquisabinene and Sesquithujene

The use of propargyl esters in total synthesis as an alternative to diazo compounds was further outlined by Fürstner in the synthesis of Sesquisabinene and Sesquithujene terpenoids.⁴⁷ Fürstner's approach consisted in the asymmetric synthesis of two key diastereomeric intermediates *via* a gold-catalyzed transformation in which the propargylic stereocentre of the substrate is converted into the cyclopropane unit of the expected bicyclo[3.1.0]ketone framework with high diastereoselectivity (*Scheme 30*).⁴⁸

AuCl₃(pyridine)-catalyzed cycloisomerization of each precursor, followed by hydrolysis of the enol ester, furnished the desired [3.1.0]bicyclohexane derivatives. Then, treatment with Ph₃P=CH₂ in THF afforded (-)-Sesquisabinene in 69% yield, the spectroscopic data of which were in full agreement with those previously reported in the literature (*Scheme 30*, upper part). On the other hand, the iron-catalyzed cross-coupling of the enol triflate of the diastereomeric compound provided (-)-Sesquithujene in 58% yield over both steps (*Scheme 30*, bottom part). The products so formed can correspond to either the natural compounds or their enantiomers, since the rotatory power of the natural products is lacking in the literature.

⁴⁷ Terhune, S.J., Hogg, J.W., Bromstein, A.C., Lawrence, B.M. *Can. J. Chem.* **1975**, *53*, 3285-3293.

⁴⁸ Fürstner, A., Schlecker, A. *Chem. Eur. J.* **2008**, *14*, 9181-9191.



Scheme 30 Syntheses of (-)-Sesquisabinene and Sesquithujene

4. Frondosin A

The formal enantioselective synthesis of marine norsesquiterpenoid (-)-Frondosin A⁴⁹ *via* a gold-catalyzed 1,2-acyloxy-rearrangement/cyclopropanation/cycloisomerization cascade⁵⁰ constitutes a beautiful expansion of the concept presented above as well as a nice alternative to cycloaddition reactions devised up to now for the construction of seven-membered rings.⁵¹

Several approaches towards the core of the frondosins had previously been disclosed in the literature, including one enantioselective total synthesis of (+)-Frondosin A.⁵² In the present case, the desired bicyclic cycloheptenyl ester was formed quantitatively by treatment of pivaloate **126** and 6,6-dimethyl-1-vinyl cyclohexene **127** with (S)-OMe-DTBM-BIPHEPAu₂]Cl₂. *In situ* hydrolysis followed by equilibration with NaOMe/MeOH afforded the thermodynamically favoured bicyclic enone **128**, which was recently elaborated into Frondosins A and B (Scheme 31).⁵³

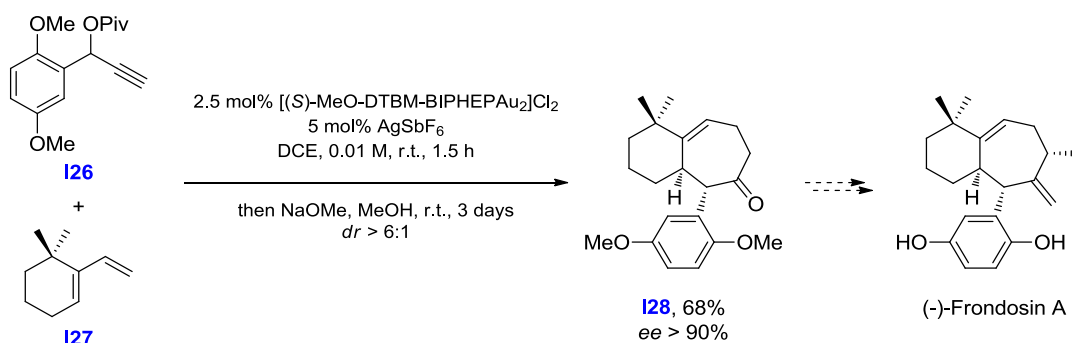
⁴⁹ (-)-Frondosin A features promising biological activities: Patil, A.D., Freyer, A.J., Killmer, L., Offen, P., Carte, B., Jurewicz, A.J., Johnson, R.K. *Tetrahedron* **1997**, *53*, 5047-5060; Hallock, Y.F., Cardellina, J.H., Boyd, M.R. *Nat. Period. Lett.* **1998**, *11*, 153-160.

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

⁵¹ Battiste, M.A., Pelphrey, P.M., Wright, D.L. *Chem. Eur. J.* **2006**, *12*, 3438-3447; Wegner, H.A., De Meijere, A., Wender, P.A. *J. Am. Chem. Soc.* **2005**, *127*, 6530-6531; Wender, P.A., Haustedt, L.O., Lim, J., Love, J.A., Williams, T.J., Yoon, J.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 6302-6303, and references therein; Davies, H.M.L., Denton, J.R. *Chem. Soc. Rev.* **2009**, *38*, 3061-3071; Lian, Y., Miller, L.C., Born, S., Sarpong, R., Davies, H.M.L. *J. Am. Chem. Soc.* **2010**, *132*, 12422-12425.

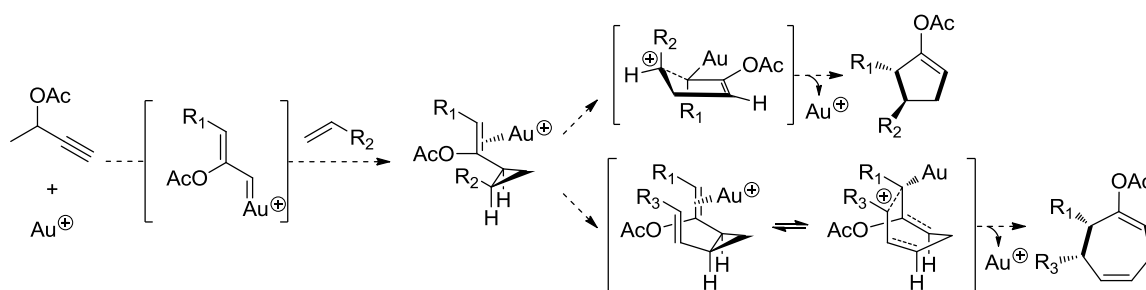
⁵² Trost, B.M., Hu, Y., Home, D.B. *J. Am. Chem. Soc.* **2007**, *129*, 11781-11790.

⁵³ Xin, L., Keon, A.E., Sullivan, J.A., Ovaska, T.V. *Org. Lett.* **2008**, *10*, 3287-3290; Ovaska, T.V., Sullivan, J.A., Ovaska, S.I., Winegrad, J.B., Fair, J.D. *Org. Lett.* **2009**, *11*, 2715-2718.



Scheme 31 Formal Enantioselective Synthesis of (-)-Fronodosin A

The proposed mechanism is depicted below. The gold-mediated isomerization of the propargyl ester leads to a gold carbenoid which reacts with the olefin to form a *cis*-cyclopropane intermediate. Subsequent reactivation of the vinyl acetate by gold triggers the cyclopropyl ring-opening, thus forming a 1,5-dipole. An envelope conformation was proposed by the authors for the transition state, in which substituents are disposed in a *trans*-pseudoaxial fashion to minimize torsional/steric interactions, so that the *trans*-2,3-disubstituted cyclopentannulation product is obtained (Scheme 32, upper part). In contrast, when a 1,4-diene is used instead of an olefin, the cyclopropyl system undergoes a gold-catalyzed Cope rearrangement to deliver the *cis*-2,3-disubstituted cycloheptenyl acetate. A boatlike transition state was proposed in this case to account for the observed *cis* relative stereochemistry (Scheme 32, bottom part).



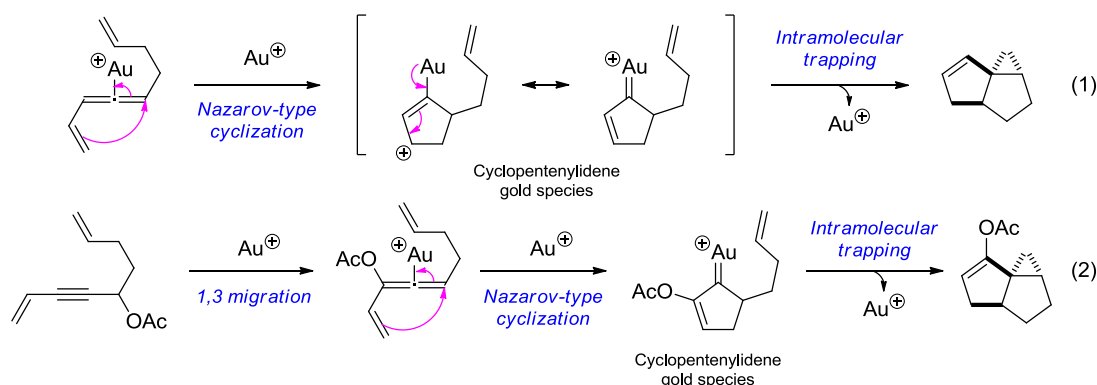
Scheme 32 Mechanistic Proposal for the Gold-catalyzed 1,2-acyloxy-rearrangement/cyclopropanation/cycloisomerization cascade

5. $\Delta^{9(12)}$ -Capnellene

In 2009, Fensterbank and co-workers reported the generation and intramolecular trapping of cyclopentenylidene gold species from the cycloisomerization of ene vinyl allenes through a Nazarov-type cyclization (Scheme 33, equation (1)).⁵⁴ They further envisioned that acetates could themselves give rise to the same kind of transformation. Indeed, the

⁵⁴ Lemière, G., Gandon, V., Cariou, K., Hours, A., Fukuyama, T., Dhimane, A.-L., Fensterbank, L., Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993-3006.

rearrangement of propargyl acetates into allenyl esters provides the vinyl allene moiety exhibiting the required substitution pattern for the next step (Scheme 33, equation (2)).



Scheme 33 Gold-catalyzed Cycloisomerization of Vinyl Ene Allenes (Equation (1)) and Vinyl Ene Propargyl Acetates via Metalla-Nazarov and Electrophilic Cyclopropanation (Equation (2))

The latter strategy was applied to the total synthesis of $\Delta^{9(12)}$ -Capnellene, a marine sesquiterpene of the capnellane family isolated from *Capnella imbricata* in 1978.⁵⁵ Many synthetic ways to this product had previously been reported,⁵⁶ including enantioselective ones.⁵⁷ In most syntheses, the triquinane skeleton was obtained in several steps *via* a diquinane system; quite a few propose the formation of the tricyclopentanoid framework in one step.⁵⁸ The propargyl acetate precursor to the gold-catalyzed reaction was prepared in 67% over 6 steps, and obtained as a 1:1 mixture of diastereomers. In the presence of 2 mol % of Echavarren's catalyst, the expected triquinane **129** was obtained, also as a 1:1 mixture of diastereomers, and

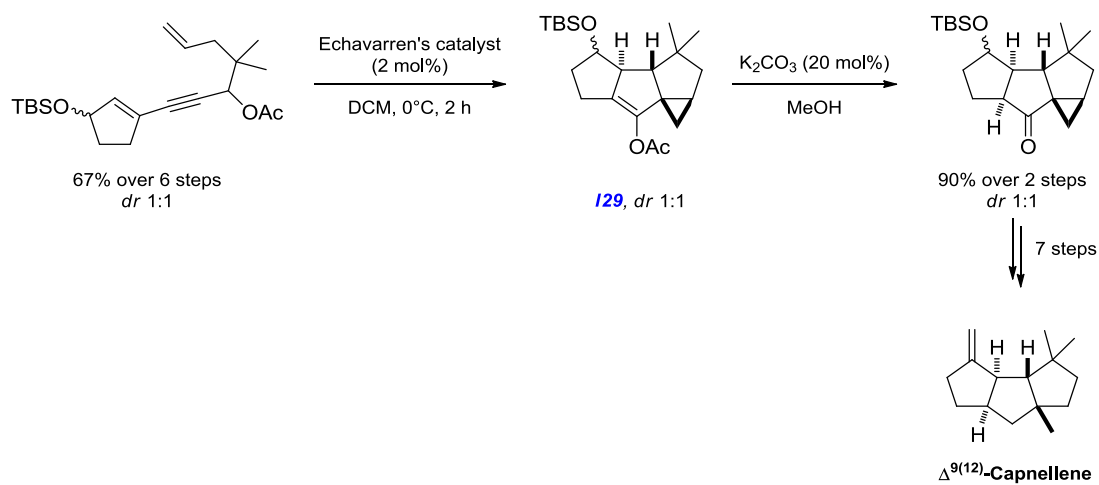
⁵⁵ Ayanoglu, E., Gebreyesus, T., Beechan, C.M., Djerassi, C., Kaisin, M. *Tetrahedron Lett.* **1978**, 1671.

⁵⁶ Stevens, K. E., Paquette, L. A. *Tetrahedron Lett.* **1981**, 22, 4393; Birch, A. M., Pattenden, G. *Tetrahedron Lett.* **1982**, 23, 991; Fujita, T., Ohtsuka, T., Shirahama, H., Matsumoto, T. *Tetrahedron Lett.* **1982**, 23, 4091; Oppolzer, W., Battig, K. *Tetrahedron Lett.* **1982**, 23, 4669; Huguet, J., Karpf, M., Dreiding, A. S. *Helv. Chim. Acta.* **1982**, 65, 2413; Piers, E., Karunaratne, V. *Can. J. Chem.* **1984**, 62, 629; Crisp, G. T., Scott, W. J., Stille, J. K. *J. Am. Chem. Soc.* **1984**, 106, 7500; Liu, H. J., Kulkarni, M. G. *Tetrahedron Lett.* **1985**, 26, 4847; Stille, J. R., Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, 108, 855; Iyoda, M., Kushida, T., Kitami, S., Oda, M. *J. Chem. Soc., Chem. Commun.* **1987**, 1607; Uyehara, T., Furuta, T., Akamatsu, M., Kato, T., Yamamoto, Y. *J. Org. Chem.* **1989**, 54, 5411; Ihara, M., Suzuki, T., Katogi, M., Taniguchi, N., Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1991**, 646; Gambacorta, A., Fabrizi, G., Bovicelli, P. *Tetrahedron Lett.* **1992**, 48, 4459; Shono, T., Kise, N., Fujimoto, T., Tominaga, N., Morita, H. *Tetrahedron Lett.* **1992**, 57, 7175; Tanaka, K., Ogasawara, K. *Chem. Commun.* **1996**, 1839; Singh, V., Prathap, S., Porinchu, M. *Tetrahedron Lett.* **1997**, 38, 2911; Samajdar, S., Patra, D., Ghosh, S. *Tetrahedron* **1998**, 54, 1789.

⁵⁷ Meyers, A. I., Bienz, S. *J. Org. Chem.* **1990**, 55, 791; Sonawane, H. R., Nanjundian, B. S., Shah, V. G., Kulkarni, D. G., Ahuja, J. R. *Tetrahedron Lett.* **1991**, 32, 1107; Ohshima, T., Kagechika, K., Adachi, M., Sodeoka, M., Shibasaki, M. *J. Am. Chem. Soc.* **1996**, 118, 7108.

⁵⁸ Little, R. D., Carroll, G. L. *Tetrahedron Lett.* **1981**, 22, 4389; Mehta, G., Reddy, D. S., Murty, A. N. *J. Chem. Soc., Chem. Commun.* **1983**, 824; Curran, D. P., Chen, M.-H. *Tetrahedron Lett.* **1985**, 26, 4991; Wang, Y., Mukherjee, D., Birney, D., Houk, K. N. *J. Org. Chem.* **1990**, 55, 4504; Balme, G., Bouyssi, D. *Tetrahedron* **1994**, 50, 403.

directly converted into the corresponding ketones in 90% yield over the two steps. $\Delta^{9(12)}$ -Capnellene was then obtained in 7 steps (Scheme 34).



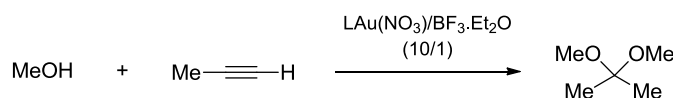
Scheme 34 Total Synthesis of $\Delta^{9(12)}$ -Capnellene via 3,3-rearrangement, Metalla-Nazarov and Electrophilic Cyclopropanation

Chapter II - Development of New Ligands for Gold Catalysis

Even though the use of simple gold(I) and gold(III) salts such as AuCl, AuCl₃ and NaAuCl₄ has been reported, most studies employ gold(I) chloride complexes bearing a monodentate ancillary ligand, [(PPh₃)AuCl] certainly being the most frequently encountered catalyst.⁵⁹

Ligands play a major role in tuning the reactivity in transition metal catalysis. Buchwald's palladium-catalyzed reactions such as amination,⁶⁰ fluorination,⁶¹ and trifluoromethylation of aryl halides or triflates⁶² are remarkable examples.

Ligand effects on the gold cationic center have been noted since the work of Teles, in which it is shown that the activity of the catalyst in the hydration of alkynes is inversely correlated to the Lewis basicity of the ligand (Table 1).⁶³ Thus, triphenylphosphite led to the most electrophilic cationic complex (Table 1, entry 6, initial TOF 1500 h⁻¹), which was also the most active in terms of turnover but the less stable, being rapidly deactivated (Table 1, entry 6, TON 2500).



Entry	Ligand	Initial TOF (h ⁻¹)	TON
1	AsPh ₃	430	-
2	PEt ₃	550	-
3	PPh ₃	610	>5000
4	P(4-F-Ph) ₃	640	-
5	P(4-OMe-Ph) ₃	1200	-
6	P(OPh) ₃	1500	2500

Table 1 Hydroalkoxylation of Propyne

Though a lot of empirical information on ligand effects in homogeneous gold catalysis is available, the outcome of the reaction is still often unpredictable. A recent report by Xu and co-workers shows through kinetic analyses how the electronic properties of the ligand can affect

⁵⁹ Reviews: Hashmi, A.S.K., Hutchings, G.J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7896-7936; Hashmi, A.S.K. *Chem. Rev.* **2007**, *107*, 3180-3211.

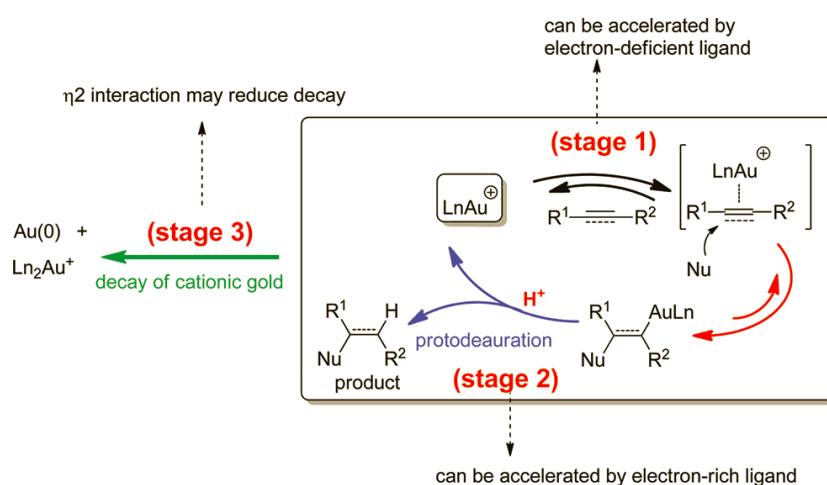
⁶⁰ Fors, B.P., Watson, D.A., Biscoe, M.R., Buchwald, S.L. *J. Am. Chem. Soc.* **2008**, *130*, 13552.

⁶¹ Watson, D.A., Su, M., Teverovskiy, G., Zhang, Y., Garcia-Fortanet, J., Kinzel, T., Buchwald, S.L. *Science* **2009**, *325*, 1661.

⁶² Cho, E.J., Senecal, T.D., Kinzel, T., Zhang, Y., Watson, D.A., Buchwald, S.L. *Science* **2010**, *328*, 1679.

⁶³ Teles, J.H., Brode, S., Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1215-1418.

the kinetics of the three major stages of the catalytic cycle involved in a series of gold-catalyzed prototypical reactions, such as propargyl amide cyclization, hydroamination of alkynes and allenyl ester isomerization (Scheme 35).⁶⁴ The first stage consists in the electrophilic activation of either the alkyne or the allene partner and is logically favoured by less electron-donating ligands. The second stage is the protodeauration, which in contrast is accelerated by electron-donating ligands. The third stage is the catalyst deactivation, which according to the work of Echavarren may be avoided by a η^2 interaction between the cationic gold centre and the double bond of an arene. This would account for the higher stability of biphenyl gold(I) complexes involving Buchwald-type phosphines, for instance *tert*butylXPhos or JohnPhos.



Scheme 35 Gold Catalytic Cycle

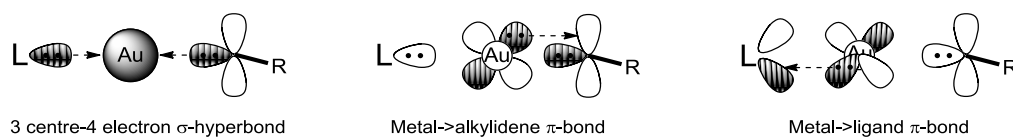
Toste rationalized the impact of the ligand on reactivity in terms of degrees of σ - and π -bonding in gold-stabilized cationic intermediates.⁶⁵ According to this study, the L-Au-C bonding can be partitioned into three components (Scheme 36).⁶⁶ Given the electronic configuration of gold(0) ($[\text{Xe}]4f^{14}5d^{10}6s^1$), only one valence orbital (6s) is vacant on gold(I). In agreement with Pauli exclusion principle, a three centre-four-electron σ -hyperbond must therefore be formed for the L-Au-C triad as $[\text{L}:\text{Au}-\text{C} \leftrightarrow \text{P}-\text{Au}:\text{C}]$. Hence, the Au-C bond order decreases with increasing *trans* ligand σ -donation (*trans* effect) (Scheme 36, left). In addition, the metal centre is able to form two π -bonds by donation from perpendicular filled d-orbitals into empty π -acceptors on the substrate (Scheme 36, middle) and the ligand (Scheme 36, right). Though these two bonds

⁶⁴ Wang, W., Hammond, G.B., Xu, B. *J. Am. Chem. Soc.* **2012**, *134*, 5697-5705.

⁶⁵ Benitez, D., Shapiro, N.D., Tkatchouk, E., Wang, Y., Goddard III, W.A., Toste, F.D. *Nature Chem.* **2009**, *1*, 482-486; Gorin, D.J., Sherry, B.D., Toste, F.D. *Chem. Rev.* **2008**, *108*, 3351-3378.

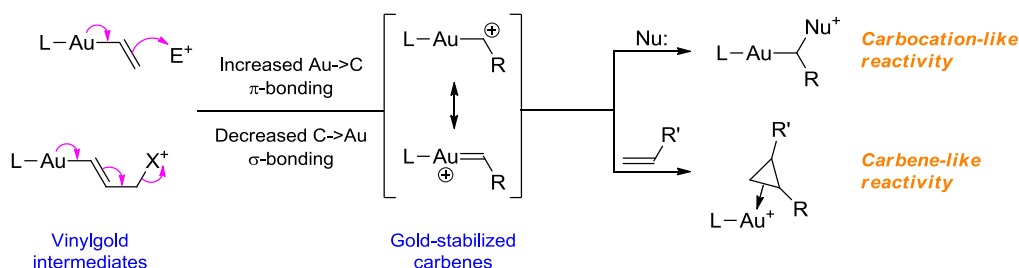
⁶⁶ Dewar, M. *Bull. Soc. Chim. Fr.* **1951**, *18*, C71-C77; Chatt, J., Duncanson, L.A. *J. Chem. Soc.* **1953**, 2939-2947.

are not mutually exclusive, they do compete for electron density from gold, thus rendering the strength of the back-donation to the substrate dependent on the nature of the ancillary ligand.



Scheme 36 Most Important Bonding Interactions in L-Au(I)-CR₂⁺

Gold-stabilized carbene intermediates possess highly electron-deficient α -carbons that are stabilized, to varying degrees, by back donation from the metal to the vacant π -orbital of the singlet carbene. This electron deficiency reduces donation from the filled sp^2 σ -orbital of the carbene to the metal, therefore minimizing carbon-gold σ -bonding (*Scheme 37*). This suggests that the conversion of a vinylgold intermediate into a gold-stabilized carbene, as commonly proposed in gold-catalyzed reactions,⁶⁷ occurs with an increase in gold-carbon π -bonding and a decrease in the σ -bonding. The bonding situation in these carbene intermediates is often depicted by two extreme resonance structures: a carbocation with a gold-carbon single bond (*Scheme 37*, upper part) or a carbene with a gold-carbon double bond (*Scheme 37*, bottom part). Strongly π -acidic ligands are expected to increase carbocation-like reactivity by decreasing gold-to-substrate π -donation (*Scheme 37*, upper part). Conversely, strongly σ -donating ligands are expected to increase carbene-like reactivity (*Scheme 37*, bottom part). Worthy of note, divergence towards carbocation-like or carbene-like reactivity may also be influenced by the potential of the nucleophile to intercept the developing positive charge.



Scheme 37 Conversion of Vinylgold Intermediates into Gold-stabilized Carbenes

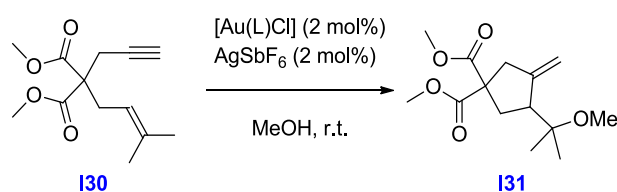
In the past decade, great effort has been made in developing suitable ligands to achieve better efficiency and selectivity in gold catalysis. Especially, phosphanes and N-heterocyclic

⁶⁷ Mamane, V., Gress, T., Krause, H., Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654-8655; Luzung, M.R., Markham, J.P., Toste, F.D. *J. Am. Chem. Soc.* **2004**, *126*, 10858-10859; Gorin, D.J., Davis, N.R., Toste, F.D. *J. Am. Chem. Soc.* **2005**, *127*, 1126-1127; Nieto-Oberhuber, C., Munoz, M.P., Bunuel, E., Nevado, C., Cardenas, D.J., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406; Shapiro, N.D., Toste, F.D. *J. Am. Chem. Soc.* **2007**, *129*, 4160-4161; Zhang, G., Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 12598-12599.

carbenes (NHC) have emerged as privileged ligands for gold(I)-catalyzed reactions. Representative examples of ligands developed with a view to tune efficiency and/or selectivity are presented below.

I. Biphenylphosphine-Gold(I) Complexes

Bulky biphenylphosphane ligands have been particularly successful in Pd-catalyzed reactions.⁶⁸ Subsequently, Echavarren *et al.* reasoned that higher reactivity could similarly be achieved in gold catalysis by using bulkier phosphines, and reported highly reactive cationic biphosphine Au(I) complexes.⁶⁹ The catalytic efficiency of the new catalysts 1a-d was evaluated in the methoxycyclization of 1,6-enyne **130**. With either electron rich or electron poor phosphines such as PCy₃, PPh₃ or P(C₆F₅)₃, the expected product **131** was formed in uniformly good yields within 5 h (*Table 2, entry 1*). With bulkier phosphines like P(o-Tol)₃ or P(1-Naphth)₃, slower reactions were observed (*Table 2, entries 2-3*). In contrast, **131** was obtained within 30 minutes only when biphenyl-based phosphines were used (*Table 2, entries, 4-5*). Comparatively, Au(I) complexes with NHC donor ligands were less active (*Table 2, entries 6-8*).

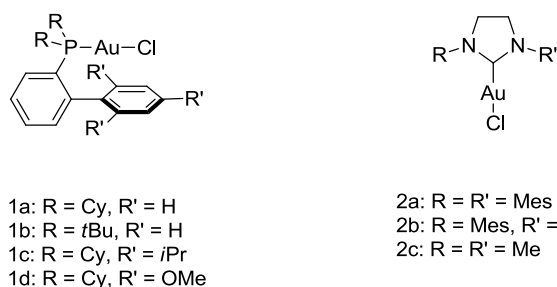


Entry	[Au(I)]	Time (h)	Yield (%)
1	[Au(PPh ₃)Cl]	3	84
2	[AuP(o-Tol) ₃ Cl]	24	90
3	[AuP(1-Naphth) ₃ Cl]	18	76
4	1a	0.5	97
5	1b-d	0.25	89-92
6	2a	1.5	71
7	2b	5	87
8	2c	24	34

Table 2 Ligand Effect on the Cycloisomerization of 1,6-Enyne 130

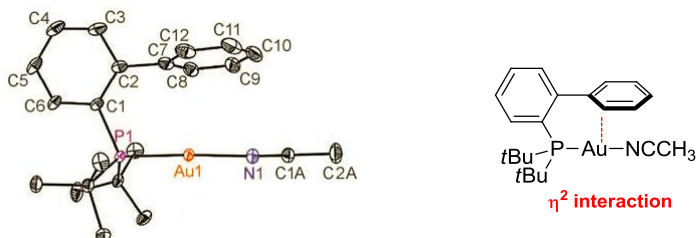
⁶⁸ Walker, S.D., Border, T.E., Martinelli, J.R., Buchwald, S.L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871-1876; Kaye, S., Fox, J.M., Hicks, F.A., Buchwald, S.L. *Adv. Synth. Catal.* **2001**, *343*, 789-794.

⁶⁹ Nieto-Oberhuber, C., Lopez, S., Echavarren, A.M. *J. Am. Chem. Soc.* **2005**, *127*, 6178-6179.



Scheme 38 Biphenylphosphine-gold(I) Complexes (Left) and NHC-gold(I) Complexes (Right)

In view of the unusual Pd-arene interactions found in biphenyl-based palladium(I) complexes,⁷⁰ Echavarren prepared stable cationic complexes $[\text{Au}(\text{PR}_3)(\text{L})]^+ \text{A}^-$ (L = ligand) with $\text{A}^- = \text{AgSbF}_6^-$ as a weakly coordinating counteranion and an acetonitrile ligand. Especially, complexes $[\text{AuP}(\text{Cy})_2(\text{o-biPh})]^+ \text{SbF}_6^-$ and $[\text{AuP}(\text{tBu})_2(\text{o-biPh})]^+ \text{SbF}_6^-$ have been crystallized, thus revealing weak η^2 interactions between the Au centre and the arene parallel to the P-Au bond (average distance between the Au centre and the covering arene: 3.03 Å) (Scheme 39).⁷¹ Worthy of note, the prepared biphenylphosphine-gold(I) complexes proved particularly active for the alkoxy cyclization, skeletal rearrangement⁷² and intramolecular cyclopropanation⁷³ of a variety of enynes. Importantly, they allow reactions to be carried out in the absence of Ag^+ , which can lead to unwanted side reactions.⁷⁴



Scheme 39 η^2 interaction between the Gold Centre and the covering Arene in $[\text{AuP}(\text{tBu})_2(\text{o-biPh})]^+ \text{SbF}_6^-$

It is worth mentioning that although JohnPhos itself is undoubtedly a rather electron-rich ligand, the electronic properties of the corresponding cationic Au(I) complex are less clear.

⁷⁰ Barder, T.E. *J. Am. Chem. Soc.* **2006**, *128*, 898-904; Christmann, U., Vilar, R., White, A.J.P., Williams, D.J. *Chem. Commun.* **2004**, 1294-1295; Christmann, D.A., Pantazis, J., Benet-Buchholz, J.E., McGrady, F., Maseras, F., Vilar, R. *J. Am. Chem. Soc.* **2006**, *128*, 6376-6390.

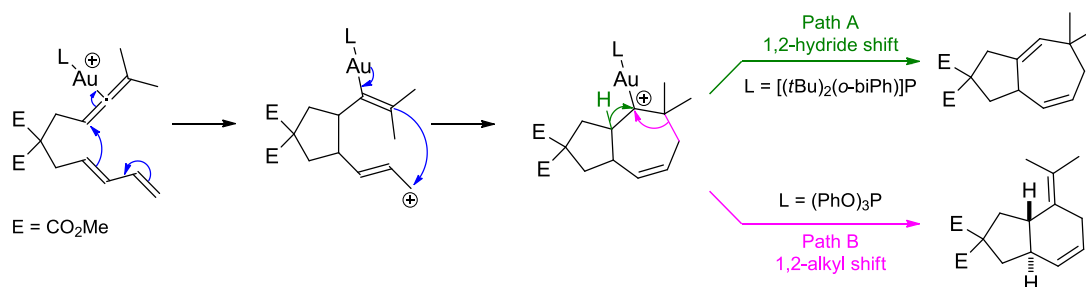
⁷¹ Herrero-Gomez, E., Nieto-Oberhuber, C., Lopez, S., Benet-Buchholz, J., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455-5459.

⁷² Nieto-Oberhuber, C., Munoz, M.P., Bunuel, E., Nevado, C., Cardenas, D.J., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406; Nieto-Oberhuber, C., Munoz, M.P., Lopez, S., Jiménez-Nunez, E., Nevado, C., Herrero-Gomez, E., Raduncan, M., Echavarren, A.M. *Chem. Eur. J.* **2006**, *12*, 1677-1693; Munoz, M.P., Adrio, J., Carretero, J.C., Echavarren, A.M. *Organometallics* **2005**, *24*, 1293-1300.

⁷³ Nieto-Oberhuber, C., Lopez, S., Munoz, M.P., Jiménez-Nunez, E., Bunuel, E., Cardenas, D.J., Echavarren, A.M. *Chem. Eur. J.* **2006**, *12*, 1694-1702.

⁷⁴ Nevado, C., Echavarren, A.M. *Chem. Eur. J.* **2005**, *11*, 3155-3164.

This was first noted by Toste, while comparing the respective behaviours of cationic gold(I) complexes of $(\text{PhO})_3\text{P}$ and $[(t\text{Bu})_2(o\text{-biPh})]\text{P}$ in the reaction of allene-dienes (*Scheme 40*).⁷⁵ In this reaction, the seven-membered ring gold-stabilized carbene originating from the [4+3] cycloaddition process is unstable and rearranges *via* 1,2-alkyl or 1,2-H shift to yield six- and seven-membered ring products respectively. On the basis of previous theoretical and experimental analyses of dialkylbiaryl phosphines,⁷⁶ Toste envisioned both electronic⁷⁷ and steric properties of the LAu^+ catalyst to affect the electronic structure of the intermediate gold-stabilized carbene and its subsequent reactivity. Specifically, Toste proposed the impact of the gold catalyst on migratory aptitude to be a consequence of the relative strength of the $d\pi$ to $\pi\pi$ interaction in the Au-C bond. The distal aryl would cause a repulsive steric interaction with the gold atom and the substrate, thus resulting in the observed distortion of the P-Au-C angle, which in complexes bearing the biarylphosphine ligand is indeed around 169° rather than 180° . This geometric distortion would reduce the Au- $d\pi$ overlap. The 1,2-alkyl shift involves both σ and π character in the carbene, thus being relatively insensitive to ligand effects, whereas results suggest that the barrier for the 1,2-H shift is affected by increased population in the C $\pi\pi$ -orbital by donation from the Au $d\pi$ -electrons.⁷⁸



Scheme 40 Proposed Mechanism for the Formation of Formal [4+3] and [3+2] Cycloaddition Products of Allenedienes

In agreement with the work of Toste, Barriault later reported that the selectivity of the gold-catalyzed cyclization of silylenol ethers can be modified when using XPhos or Me_4XPhos as the ligand. For instance, treatment of enyne **132** with IPr gives the 5-exo-dig cyclization product **133** as the major product (*Scheme 41*, left), whereas the replacement of IPr by Me_4XPhos results

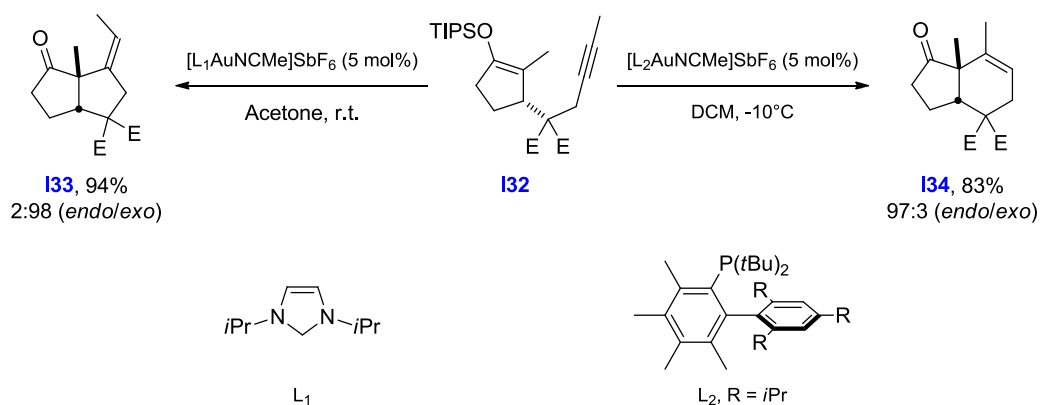
⁷⁵ Benitez, D., Tkatchouk, E., Gonzalez, A.Z., Goddard III, W.A., Toste, F.D. *Org. Lett.* **2009**, *11*, 4798-4801.

⁷⁶ Barder, T.E., Buchwald, S.L. *J. Am. Chem. Soc.* **2007**, *129*, 5096; Herrero-Gomez, E., Nieto-Oberhuber, C., Lopez, S., Benet-Buchholz, J., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455.

⁷⁷ Benitez, D., Shapiro, N.D., Tkatchouk, E., Wang, Y., Goddard III, W.A., Toste, F.D. *Nature Chem.* **2009**, *1*, 482; Gorin, D.J., Toste, F.D. *Nature* **2007**, *446*, 395.

⁷⁸ Similar effects have been calculated for transition states for 1,2-H shifts of singlet carbenes. See: Keating, A.E., Garcia-Garibay, M.A., Houk, K.N. *J. Phys. Chem. A* **1998**, *102*, 8467, and references cited therein; Albu, T.V., Lynch, B.J., Truhlar, D.G., Goren, A.C., Hrovat, D.A., Borden, W.J., Moss, R.A. *J. Phys. Chem. A* **2002**, *106*, 5323.

in an inversion of selectivity favouring the 6-*endo*-dig product **134** (Scheme 41, right). However, erosion of the *endo* selectivity was observed with electron-deficient alkynes. These divergent regioselectivities were explained in terms of steric and electronic properties of the ancillary ligand. From a steric point of view, Barriault hypothesized that an increase of steric interactions between R1 and the Au(I) complex by having bulkier ligands on the metal could disfavour the 5-*exo*-dig cyclization. From an electronic point of view, it was assumed that bulkiness of the Buchwald ligand could deform the P-Au-C angle at the transition state, which would result in a reduction of the Au- $d\pi$ ->C- $p\pi$ overlap. As a consequence, this would imply a cationic type mechanism where a partial positive charge at C1 is formed at the transition state.



Scheme 41 Modulation of the Regioselectivity of the Gold-catalyzed Cyclization of Silylenol Ethers by the Choice of the Ligand

II. Tris(2,4-di-*tert*butylphenyl) phosphite gold(I) chloride

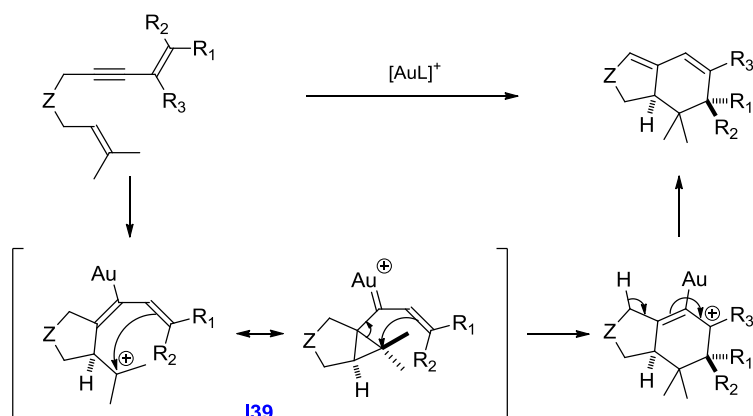
Tris(2,4-di-*tert*butylphenyl) phosphite was first introduced by Echavarren and is now routinely used as the prototype of an electron poor ligand. The corresponding gold(I) chloride complex for instance revealed exceptionally reactive in the gold-catalyzed [4+2] cycloaddition reaction of dienynes, where substantial rate accelerations were observed upon the use of this catalyst, as compared to the reactions run with Echavarren's catalyst **s43**. For example, the reaction of enynes **135** and **136** requires 2 h to be complete, whereas only 30 and 15 minutes are necessary for the expected hydrindanes **137** and **138** to be formed in good yields when {tris(2,4-di-*tert*butylphenyl) phosphite}AuCl **s45** was used.

Entry	Substrate	Catalyst	Time (min)	Products	Yields
-------	-----------	----------	------------	----------	--------

1		s43	120		52%
2		s45/AgSbF ₆	30		70%
3		s43	120		77%
4		s45/AgSbF ₆	15		71%

Table 3 gold-catalyzed [4+2] Cycloaddition Reaction of Dienes I35 and I36

Echavarren reported a DFT theoretical study on the mechanism of the reaction, which indicates that the [4+2] cycloaddition is a stepwise process, which proceeds by a 5-*exo*-dig pathway to give intermediates such as I39 which cyclize to form an allyl carbocation. This is followed by the regioselective loss of a proton which is under kinetic control and protodemetalation to give dienes (Scheme 42).



Scheme 42 Proposed Mechanism for the gold-catalyzed [4+2] Cycloaddition Reaction of Dienes

III. N-Heterocyclic Carbenes (NHCs)

NHCs offer valuable and unique electronic and steric features,⁷⁹ and revealed to be excellent ligands for transition metals, thus constituting a serious alternative to phosphine

⁷⁹ Arduengo, A.J., Bertrand, G. *Chem. Rev.* **2009**, *109*, 3209-3210; "N-Heterocyclic Carbenes in Transition Metal Catalysis" in *Top. Organomet. Chem.* (Ed.: F. Glorius), vol. 21, Springer-Verlag, Berlin/Heidelberg **2007**; Hahn, F.E., Jahnke, M.C. *Angew. Chem. Int. Ed.* **2008**, *47*, 3122-3172; Melaimi, M., Soleilhavoup, M., Bertrand, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 8810-8849; Dröge, T., Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 6940-6952.

ligands.⁸⁰ On the one hand, these ligands are stabilized by electronic donation from the filled orbitals of the two nitrogens into the empty p orbital of the carbenic carbon. On the other hand, electroattracting inductive effect from nitrogens stabilizes the carbene lone pair. These two electronic effects together are responsible for the stability and strongly σ -donating character of NHCs. Thus, NHC-M bonds are usually stronger than the corresponding bonds with phosphines,⁸¹ so that there is no decoordination, and complexes are more stable to temperature, humidity and air.⁶⁸ The π -acceptor properties of NHCs, however, are usually considered weak, though they can efficiently be modulated.⁸²

From a steric point of view, NHCs and phosphines exhibit very distinct properties. On phosphine complexes, R substituents are linked directly to the phosphorus and form a cone. The substituents on P are not directed toward the metal. On the contrary, NHCs form a pocket around the metal. Thus, the nature of R substituents on the nitrogen strongly impact on steric hindrance.⁸³ The size of phosphine ligands can be measured by the cone angle θ proposed by Tolman.⁸⁴ With NHCs, however, steric parameter calculations using the Tolman model have proven difficult and sometimes meaningless. Therefore, Nolan and Cavallo proposed another model to measure the steric bulk of NHC ligands: the "Percent buried volume" ($\%V_{bur}$).⁸⁵

During the past years, NHCs have become advantageous in a number of catalytic processes and have impacted upon all fields of organometallic chemistry.⁶⁸ Usually, they do impart to transition metals both high stability and enhanced reactivity. Particularly impressive results were for instance obtained with ruthenium complexes designed for metathesis, in which phosphine PCy_3 (Grubbs catalyst, 1st generation)⁸⁶ was replaced with a NHC ligand (Grubbs catalyst, 2nd generation).⁸⁷

It was inevitable that these appealing ligands meet the high potential of gold. In 2003, Herrmann reported the first example of catalytic use of an NHC-gold complex for the hydration

⁸⁰ Diez-Gonzalez, S., Marion, N., Nolan, S.P. *Chem. Rev.* **2009**, *109*, 3612-3676; Herrmann, W.A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290-1309; Bedford, R.B., Cazin, C.S.J., Holder, D. *Coord. Chem. Rev.* **2004**, *248*, 2283-2321.

⁸¹ Cavallo, L., Correa, A., Costabile, C., Jacobsen, H. *J. Organomet. Chem.* **2005**, *690*, 5407-5413.

⁸² Alcazaro, M., Stork, T., Anoop, A., Thiel, W., Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2542-2546; Fürstner, A., Alcazaro, M., Krause, H., Lehmann, C.W. *J. Am. Chem. Soc.* **2007**, *129*, 12676-12677.

⁸³ Huang, J., Schanz, H.J., Stevens, E.D., Nolan, S.P. *Organometallics* **1999**, *18*, 2370.

⁸⁴ Tolman, C.A. *Chem. Rev.* **1977**, *77*, 313-348.

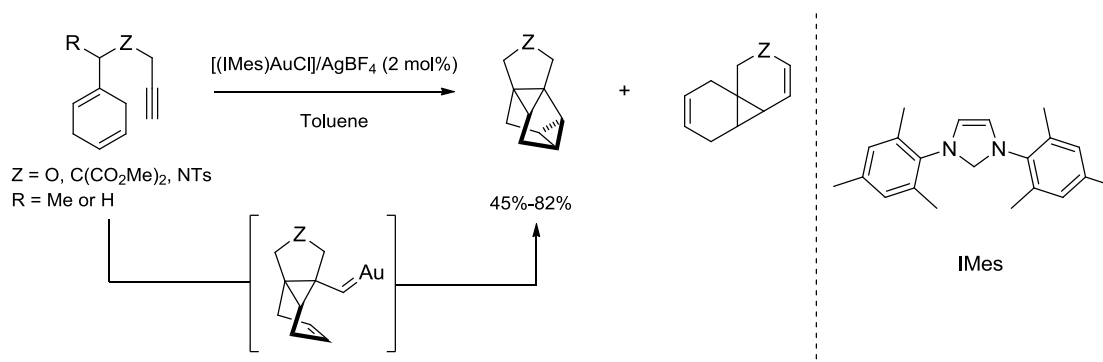
⁸⁵ Hillier, A.C., Sommer, W.J., Yong, B.S., Petersen, J.L., Cavallo, L., Nolan, S.P. *Organometallics* **2003**, *22*, 4322-4326; Clavier, H., Nolan, S.P. *Chem. Commun.* **2010**, *46*, 841-861. For more information on the percent buried volume, see chapter IV.

⁸⁶ Nguyen, S.T., Johnson, L.K., Grubbs, R.H., Ziller, J.W. *J. Am. Chem. Soc.* **1992**, *114*, 3974-3975; Nguyen, S.T., Grubbs, R.H., Ziller, J.W. *J. Am. Chem. Soc.* **1993**, *115*, 9858-9859; Schwab, P., France, M.B., Ziller, J.W., Grubbs, R.H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039-2041.

⁸⁷ Scholl, M., Trnka, T.M., Morgan, J.P., Grubbs, R.H. *Tetrahedron Lett.* **1999**, *40*, 2247-2250; Scholl, M., Ding, S., Lee, W.C., Grubbs, R.H. *Org. Lett.* **1999**, *1*, 953-956; Chatterjee, A.K., Grubbs, R.H. *Org. Lett.* **1999**, *1*, 1751-1753.

of an alkyne.⁸⁸ This was followed, in 2005, by Nolan's versatile preparation of various N-heterocyclic carbene-gold(I) complexes. These seminal publications terminated an era of sporadic reports on various gold-carbene complexes and clearly inaugurated the use of these complexes in synthetic catalysis.⁸⁹ NHC gold(I/III) complexes⁹⁰ often lead to excellent results in homogeneous catalysis owing to their thermal stability and air/moisture inertness, although turnover numbers are often modest.⁹¹

The skeletal rearrangement of enynes is undoubtedly the most popular reaction in gold catalysis⁹² and yet few reports have appeared that use NHC-based gold catalysts. The intermolecular bis-cyclopropanation of 1,6-enynes with alkenes however constitutes one example of the beneficial use of NHC ligands in enyne cycloisomerization.⁹³ In this transformation, the first cyclopropanation occurs intramolecularly, leading to a cyclopropylcarbene intermediate, which is trapped by the remaining alkene to afford the bis-cyclopropyl compound (*Scheme 43*). [(IMes)AuCl] indeed outperformed tertiary phosphine and phosphite ligands both in terms of yield and selectivity. Interestingly, in the presence of an unsymmetrical diene, the second cyclopropanation occurred at the less hindered C=C bond.



Scheme 43 [(IMes)AuCl]-Catalyzed Intermolecular Bis-Cyclopropanation of Enynes with Alkenes

⁸⁸ Schneider, S.K., Herrmann, W.A., Herdtweck, E. *Z. Anorg. Allg. Chem.* **2003**, 629, 2363-2370.

⁸⁹ De Frémont, P., Scott, W.M., Stevens, E.D., Nolan, S.P. *Organometallics* **2005**, 24, 2411-2418 and references therein; Nieto-Oberhuber, C., Lopez, S., Echavarren, A.M. *J. Am. Chem. Soc.* **2005**, 127, 6178-6179.

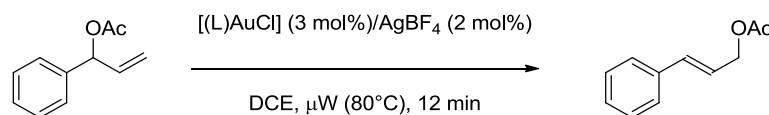
⁹⁰ For NHC-gold(III) catalysts, see: Jacques, B., Hueber, D., Hameury, S., Braunstein, P., Pale, P., Blanc, A., de Frémont, P. *Organometallics* **2014**, 33, 2326-2335; Hoffmann, M., Weibel, J.-M., de Frémont, P., Pale, P., Blanc, A. *Org. Lett.* **2014**, 16, 908-911; Orbisaglia, S., Jacques, B., Braunstein, P., Hueber, D., Pale, P., Blanc, A., de Frémont, P. *Organometallics* **2013**, 32, 4153-4164.

⁹¹ For reviews on NHCs, see: *N-heterocyclic Carbenes in Synthesis* (Ed.: S.P. Nolan), Wiley-VCH, Weinheim, **2006**; "N-Heterocyclic Carbenes in Transition Metal Catalysis": *Topics in Organometallic Chemistry, Vol. 21* (Ed.: F. Glorius), Springer, Berlin **2007**; Gatineau, D., Goddard, J.-P., Mourès-Mansuy, V., Fensterbank, L. *Isr. J. Chem.* **2013**, 53, 892-900; Marion, N., Nolan, S.P. *Chem. Soc. Rev.* **2008**, 37, 1776-1782.

⁹² For a review, see: Fürstner, A., Davies, P.W. *Angew. Chem. Int. Ed.* **2007**, 46, 3410-3449.

⁹³ Lopez, S., Herrero-Gomez, E., Pérez-Galan, P., Nieto-Oberhuber, C., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2006**, 45, 6069-6032.

In the isomerization reaction of allylic esters,⁹⁴ the key parameter seems to be the steric hindrance of the ligand rather than its electronic properties. A series of [(NHC)AuCl] precatalysts were tested and bulky ligands (ItBu, IAd) performed better than smaller ones (ITM, ICy or PPh₃) (Table 4). This was rationalized by the authors in that a bulky ligand would shield the cationic gold centre and therefore prevent decomposition. Of note, the reaction could be carried out under microwave heating, which highlights the robustness of the NHC-Au^I bond. Thus, it might be interesting to employ this type of catalyst when harsh conditions are required.




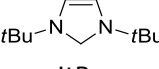
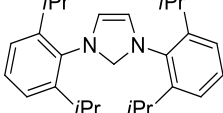
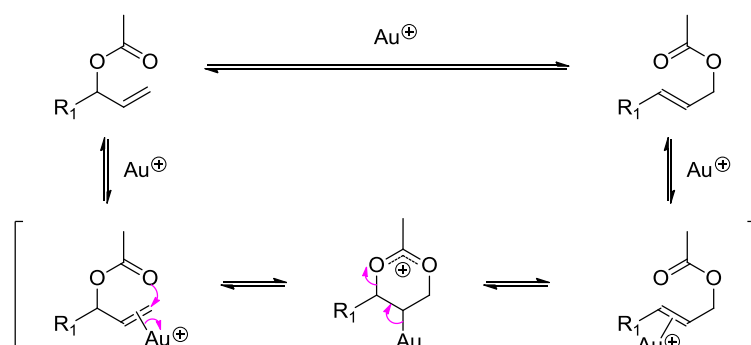
Entry	L	Yields
1	PPh ₃	53%
2		61%
3		98%
4		99%

Table 4 Ligand Effect in Au-Catalyzed Allylic Rearrangement

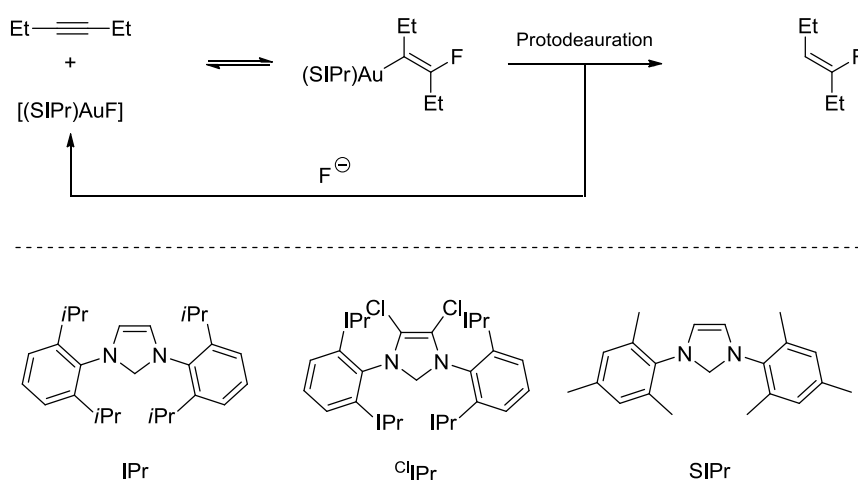
From a mechanistic standpoint, π -activation of the C=C bond triggers an intramolecular attack by the carbonyl oxygen leading to a 6-membered stabilized 1,3-acetoxonium. Regeneration of the carbonyl bond affords the isomerized olefin (Scheme 44).

⁹⁴ Marion, N., Gealageas, R., Nolan, S.P. *Org. Lett.* **2007**, 9, 2653-2656; Additions and Corrections, *Org. Lett.* **2008**, 10, 1037.



Scheme 44 Proposed Mechanism for the Au^I-catalyzed Allylic Rearrangement.

The catalytic hydrofluorination of alkynes disclosed by Sadighi⁹⁵ constitutes an additional interesting example. In a key experiment, the authors observed the formation of a likely hydrofluorination vinylgold intermediate resulting from the addition of the Au–F bond across 3-hexyne (Scheme 45). Subsequent tuning of the fluoride source and acidic media allowed the development of a catalytic transformation using [(NHC)AuCl]–AgBF₄ mixtures. It should be noted that only *trans*-hydrofluorination was observed and that ^{Cl}IPr (4,5-dichloro-1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), a less electron-rich ligand than IPr, was found to be more efficient in this reaction than IPr or SIPr.



Scheme 45 Gold-catalyzed Hydrofluorination of Hexyne (Upper Part) and Structures of IPr, ^{Cl}IPr and SIPr NHCs

IV. Cyclophanic NHCs

Whereas NHCs have indisputably excellent σ -donor qualities, their π -acceptor properties are usually considered weak. Additionally, in contrast to the phosphine series where electronic tuning can be accomplished, NHCs with different steric properties have nonetheless a similar

⁹⁵ Akana, J.A., Bhattacharyya, K.X., Müller, P., Sadighi, J.P. *J. Am. Chem. Soc.* **2007**, 129, 7736-7737.

donor ability. However, the group of Fürstner demonstrated that the course of distinct gold-catalyzed processes can be changed by the modulation of the π -acceptor properties of NHCs.⁹⁶ This is made possible by the transmission of electronic effects within a cyclophane scaffold.

New carbene **141** as well as the tetramethoxy and tetrafluoro analogues were prepared and converted into the corresponding carbonyl complexes to assess their donor properties. The stretching frequency of the *trans*-CO ligand at $\nu = 1989 \text{ cm}^{-1}$ for **141** is indicative of a donor capacity that rivals that of NHCs (Table 5, entry 2). The donor ability of the tetramethoxy-substituted carbene equals that of the unsubstituted one (Table 5, entry 3). Nevertheless, the *trans*-CO stretching frequency of the tetrafluoro-substituted carbene is significantly shifted ($\nu = 2004 \text{ cm}^{-1}$), which is indicative of a less electron-donating carbene than the unsubstituted one (Table 5, entry 4).

Entry	[Au]	R	$\nu \text{ (cm}^{-1}\text{)}$	$E_{\sigma} \text{ [eV]}$	$E_{\pi} \text{ [eV]}$	$E_{1/2} \text{ [V]}$
1	140	-	-	-4.97	-0.63	0.805
2	141	H	1989	-5.00	-1.14	0.858
3	142	OMe	1989	-4.86	-0.85	-
4	143	F	2004	-5.14	-1.34	0.905

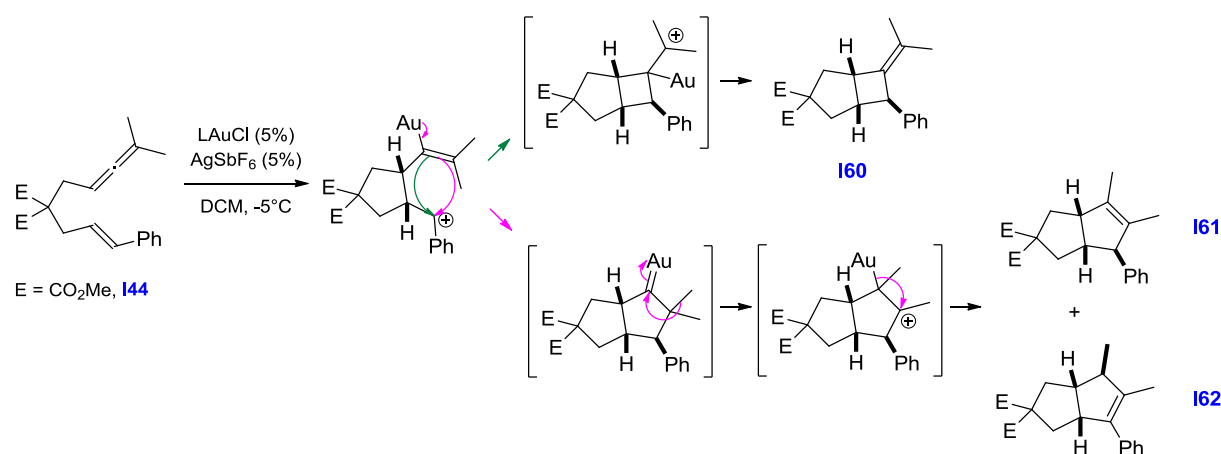
Table 5 CO Stretching Frequencies of $[\text{LRh}(\text{CO})_2\text{Cl}]$, Computed Energies of the Carbene Lone Pair (E_{σ}) and the π -Acceptor Orbital (E_{π}) and Electrochemical Redox Potential ($E_{1/2}$) of the Corresponding Rhodium Complexes of the Type $[\text{L-RhCl}(\text{cod})]$

From a computational point of view, the energy of the orbital occupied by the carbene lone pair of electrons (E_{σ}) is almost unchanged. The energy of the LUMO at the carbene center (E_{π}), however, is responsive to the nature of the NHC (with or without a cyclophane scaffold) and the type of substituents present on the benzene ring. This is indicative of an interaction between the two aromatic rings and suggests that the energy of the π -acceptor orbital can be tuned while keeping the donor capacity almost constant. Also were those results supported by electrochemical experiments, in that the π -acidity of **141** is enhanced relative to that of **140**, with their σ -donor qualities being similar, which effect augments when it comes to the tetrafluoro analogue.

Accordingly, the authors envisioned these new ligands to provide a handle to control the course of gold-catalyzed reactions. For instance, the cycloisomerization of eneallene **144** may evolve along two different pathways as a function of the electronic properties of the ligand

⁹⁶ Fürstner, A., Alcazaro, M., Krause, H., Lehmann, C.W. *J. Am. Chem. Soc.* **2007**, *129*, 12676-12677; Alcazaro, M., Stork, T., Anoop, A., Thiel, W., Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2542-2546.

coordinated to gold. Indeed, an electron-rich gold complex can stabilize an adjacent cation and therefore favour the formal [3+2] pathway (Scheme 46, bottom part), whereas a more electron-deficient catalyst favours the formation of the intermediate in which the carbenium centre is not directly bound to gold and hence delivers the alkylidenecyclobutane by a formal [2+2] cycloaddition (Scheme 46, upper part). Experimentally, complex **140** and its cyclophanic counterpart did indeed show strikingly different behaviours, with the former exclusively furnishing the [3+2] adduct whereas the better π -acceptor cyclophanic ligand gave the [2+2] adduct as the only product (Table 6, entries 1-2).



Scheme 46 Proposed Mechanism for the Formation of Allenediene **144**

Entry	Catalyst	Yields	160 : 161 + 162 ratio
1		63%	0:62+38
2		71%	100:0
3	[PPh ₃ AuCl]	83%	50:32+18

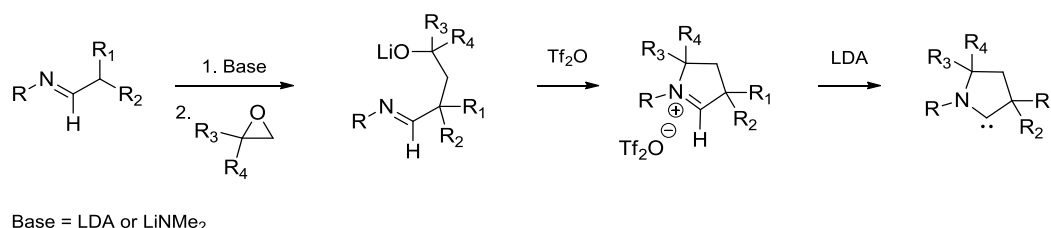
Table 6 Control over the Cycloaddition of Eneallene through Adjustment of the π -acceptor Properties of the Carbene Ligand

The π -acceptor properties of NHCs can therefore be tuned in order to control the selectivity of gold-catalyzed reactions. The main drawback of cyclophanic NHCs lies in their synthesis, which requires an important number of steps.

V. Cyclic Alkylaminocarbenes (CAAC)

Bertrand *et al.* reported that acyclic (alkyl)(amino)carbenes behave as strong σ -donors toward transition-metal centers.⁹⁷ Since NHCs are more robust and give rise to more active catalysts than their acyclic counterparts when used as ligands for transition metals, they envisioned CAACs to have interesting ligand properties as well as being more stable than their acyclic variants and thus reported the synthesis of stable cyclic (alkyl)-(amino)carbenes (CAACs),⁹⁸ in which one of the electronegative amino substituents of NHCs is replaced by a strong σ -donor alkyl group, making those ligands even more electron-rich than NHCs.

A versatile approach toward the synthesis of CAACs was designed, with R substituents potentially being anything except for H and the ring skeleton possibly modified. Deprotonation of the starting imine with LDA leads to the aza-allyl anion, which readily induces the ring opening of the epoxide. The corresponding alkoxide is obtained, which is treated with triflic anhydride at -78°C to give the triflate derivative. Warming to room temperature affords the aldiminium salt. Finally, the carbene is formed by deprotonation with LDA (*Scheme 47*).



Scheme 47 Synthesis of CAACs

Bulky and electron-rich phosphines as well as NHCs stabilize the active catalytic species. Excessive steric hindrance can nevertheless present some drawbacks.⁹⁹ In order to overcome such problems, the Glorius group developed ligands with “flexible steric bulk” using the conformational flexibility of cyclohexane (*Scheme 48*).¹⁰⁰ Owing to the presence of a quaternary carbon atom in a position α to the carbene center, CAAC carbenes feature steric environments that differentiate them dramatically from both phosphines and NHCs and amplifies the flexible

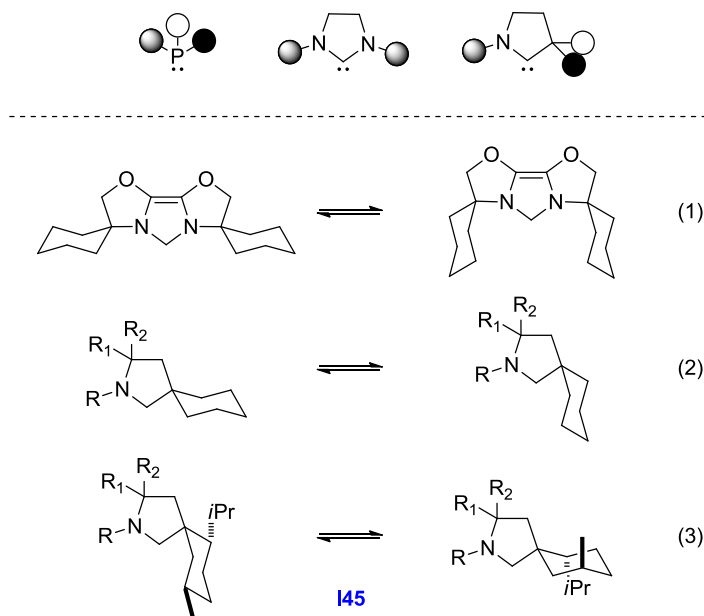
⁹⁷ Lavallo, V., Mafhouz, J., Canac, Y., Donnadieu, B., Schoeller, W.W., Bertrand, G. *J. Am. Chem. Soc.* **2004**, *126*, 8670-8671.

⁹⁸ Lavallo, V., Canac, Y., Präsang, C., Donnadieu, B., Bertrand, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 5705-5709.

⁹⁹ Gstöttmayr, C.W.K., Böm, V.P.W., Herdtweck, E., Grosche, M., Herrmann, W.A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1363.

¹⁰⁰ Altenhoff, G., Goddard, F., Lehmann, C.W., Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195; Altenhoff, G., Goddard, F., Lehmann, C.W., Glorius, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 3690.

steric bulk effect. The cyclohexane ring is closer to the carbene and metal center in the case of CAACs (Scheme 48, equation (2)). Hence, the effect of the “flexible wing” was expected to be amplified. On the contrary, rigidity can be achieved as exemplified by CAAC **145** (Scheme 48, equation (3)). Only one diastereomer is formed, and the chair conformation is locked. This offers a “wall of protection” for both the carbene and metal centre.



Scheme 48 Steric Environments of Phosphines, NHCs and CAACs (Upper Part) and Concept of Steric Bulk (Bottom Part)

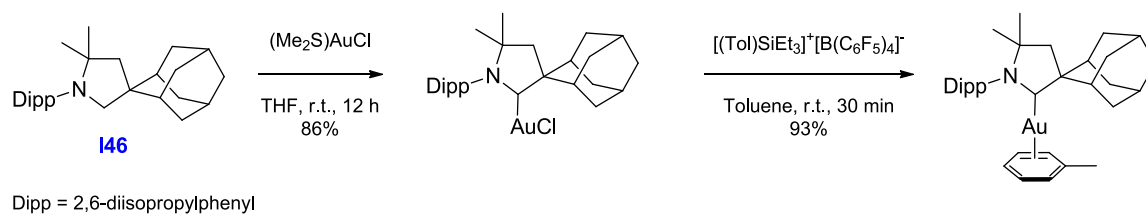
The carbonyl stretching frequencies of the iridium complexes $cis\text{-}[\text{IrCl}(\text{CO})_2(\text{L})]$ of CAACs have been measured. As a result, the average value confirms that the donor power of the CAAC is higher than that of electron-rich phosphines and NHC ligands ($\nu_{\text{av}}(\text{CO}) = 2013$ vs. 2028 and 2017–2020 cm^{-1} for PCy_3 and NHC ligands respectively).

CAAC carbenes were applied to palladium-catalyzed coupling reactions (α -arylation of ketones and aldehydes),⁸⁶ the isolation of low-coordinate rhodium and palladium complexes not isolable otherwise with any other ligands,¹⁰¹ and the synthesis of olefin metathesis catalysts.¹⁰² And because they can stabilize strongly cationic species, CAACs were envisioned to lead to the formation of robust LAu^+ catalysts. For instance, the addition of the sterically demanding spirocyclic adamantyl-substituted CAAC **146** to $\text{AuCl}(\text{SMe})_2$ followed by treatment with

¹⁰¹ Lavallo, V., Canac, Y., DeHope, A., Donnadieu, B., Bertrand, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 7236–7239.

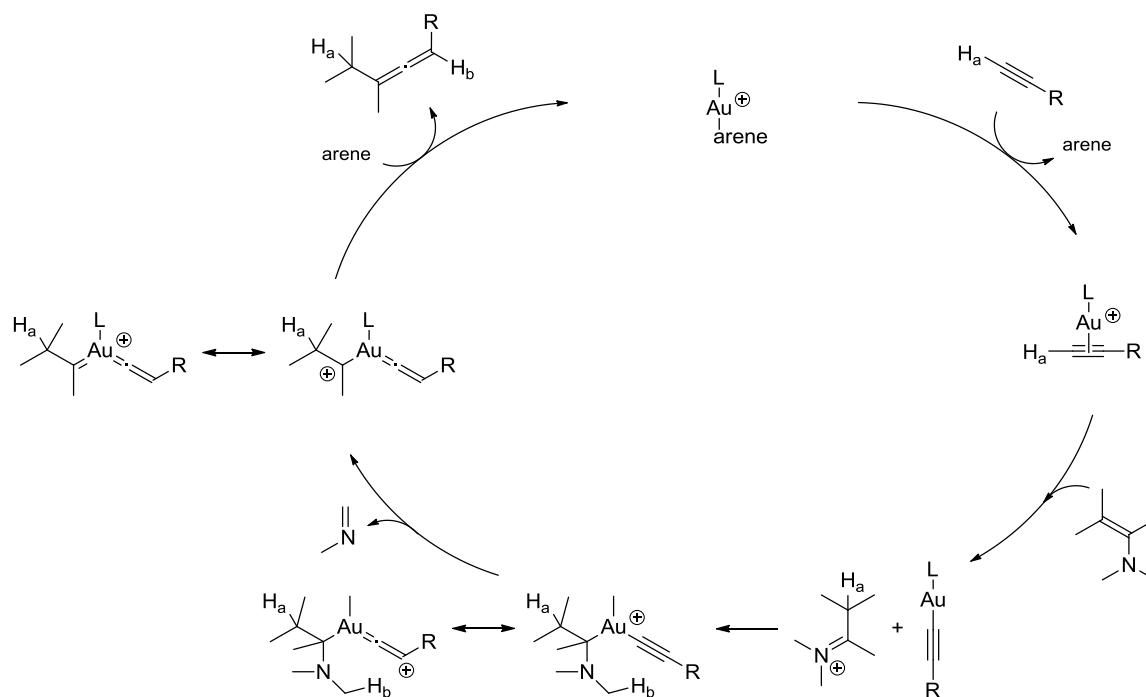
¹⁰² Anderson, D.R., Lavallo, V., O’Leary, D.J., Bertrand, G., Grubbs, R.H. *Angew. Chem. Int. Ed.* **2007**, *46*, 7262–7265.

$[\text{Et}_3\text{Si}(\text{Tol})]^+[\text{B}(\text{C}_6\text{F}_5)_4]^-$ in toluene and subsequent removal of all volatiles led to the isolable $[(\text{CAAC})\text{Au}(\eta^2\text{-toluene})]^+[\text{B}(\text{C}_6\text{F}_5)_4]^-$ complex (Scheme 49).¹⁰³



Scheme 49 Synthesis of the First CAAC-Gold Complex by Bertrand

The latter was then successfully applied to the cross-coupling of enamines and terminal alkynes to yield allenes in a diastereoselective reaction, whereas this gold-catalyzed reaction is known to usually yield propargyl amines. The reaction proceeds through a unique pathway involving Au(carbene)(vinylidene) intermediates (Scheme 50).



Scheme 50 Proposed Mechanism for the Gold-catalyzed Cross coupling Reaction of Enamines and Terminal Alkynes

Importantly, (CAAC)-gold(I) cations were also shown to readily catalyze the addition of NH_3 to non-activated alkynes and allenes.¹⁰⁴ This is remarkable, because nitrogen-carbon bonds are ubiquitous and ammonia among the least expensive bulk chemicals produced in the largest volume. To develop atom-efficient processes for the combination of NH_3 with simple organic

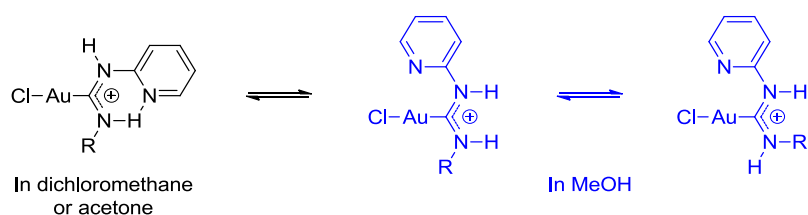
¹⁰³ Lavallo, V., Frey, G.D., Kousar, S., Donnadiou, B., Bertrand, G. *PNAS* **2007**, *104*, 13569-13573.

¹⁰⁴ Lavallo, V., Frey, G.D., Donnadiou, B., Soleilhavoup, M., Soleilhavoup, M., Bertrand, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 5224-5228.

molecules is one of the greatest challenges of synthetic chemistry, since most metals react with ammonia to afford supposedly inert Lewis acid-base complexes.¹⁰⁵

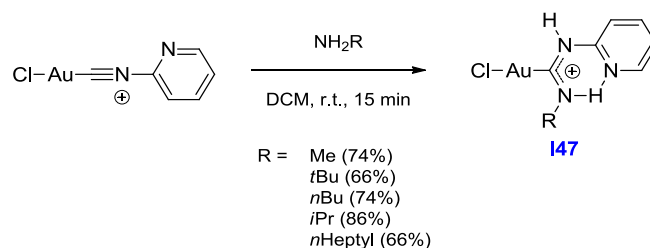
VI. Hydrogen Bond-Supported Heterocyclic Carbenes

In 2008, Echavarren and Espinet reported gold(I) complexes with hydrogen bond-supported heterocyclic carbenes (HBHCs),¹⁰⁶ the structure of which is similar to that of NHCs when in solution in dichloromethane or acetone (Scheme 51, left), but open in the presence of MeOH (Scheme 51, right). A strong intramolecular hydrogen bond produces a planar cycle reminiscent of that of NHCs, so that the R group is located close to the gold atom and may have some steric influence on the reaction.



Scheme 51 Structures of HBHCs in Dichloromethane, Acetone (Left) and MeOH (Right)

The preparation of HBHCs is straightforward. The steric requirement of the alkyl group and electronic properties of the complex can therefore easily be tuned. Gold(I) carbene complexes of the type $\text{AuCl}\{\text{C}(\text{NHR})\text{-NHPy-2}\}$ **147** are obtained by nucleophilic addition of differently hindered primary amines to pyridylisocyanide coordinated to gold (Scheme 52).



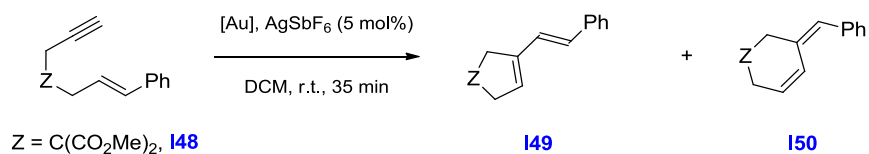
Scheme 52 Preparation of HBHCs

The catalytic performance of these new catalysts was compared to that of triphosphite gold complex **152** (Table 7, entry 4) and the highly efficient IPr **151** (Table 7, entry 3). Distinct products were obtained depending on the nature of the catalyst. While enyne **148** reacts with catalysts of type **147** to give the product of *endo* cyclization **150** as the major compound (ca. 1:3 **149**:**150**, Table 7, entries 1-2), complexes **151** and **152** favour the product of *exo* cyclization **149**

¹⁰⁵ This was first recognized by: Werner, A. Z. *Anorg. Chem.* **1893**, 3, 267.

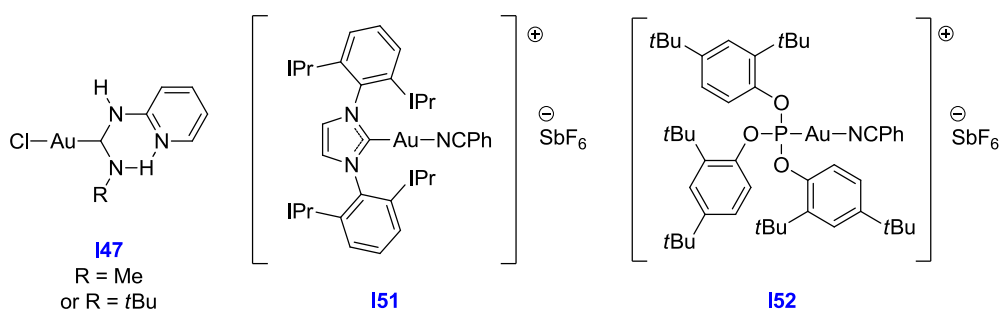
¹⁰⁶ Bartolomé, C., Ramiro, Z., Pérez-Galan, P., Bour, C., Raducan, M., Echavarren, A.M., Espinet, P. *Inorg. Chem.* **2008**, 47, 11391-11397.

(50:1 for **I51**, 73% and 2.2:1 for **I52**, 76%). For comparison, the reaction of **I48** with $[\text{Au}(\text{PPh}_3)\text{Cl}]/\text{AgSbF}_6$ gave an almost equimolar ratio of **I49**/**I50**.¹⁰⁷



Entry	Catalyst	Yields	I49 : I50 ratio
1	I47 , R = Me	100%	1:2.7
2	I47 , R = tBu	100%	1:2.8
3	I51	73%	50:1
4	I52	76%	2.2:1

Table 7 Skeletal Rearrangement of 1,6-Enyne **I48**



Scheme 53 Gold-complexes used as Catalysts for Skeletal Rearrangement of 1,6-Enyne **I48**

The cationic gold complex **I53** and the combination of **I47** (R = tBu) + AgSbF_6 provide the product of methoxycyclization **I55** in the best yields (Table 8, entries 1-2). For comparison, catalysts **I51** and **I52** (5 mol%) afford similar yields in the methoxycyclization of enyne **I54** (68 and 76%, respectively) compared to those achieved using **I47**(R = tBu)/ AgSbF_6 or **I53** (Table 8, entries 3-4). IPr and triphosphite gold complexes **I51** and **I52** led to faster reactions (30 min vs. 2-3 h) but with around 10% of methyl ketone formed *via* the formal Markovnikov addition of water to the alkyne function of **I54**. In this respect, the new catalysts were advantageous.

¹⁰⁷ Nieto-Oberhuber, C., Munoz, M.P., Lopez, S., Jiménez-Nunez, E., Nevado, C., Herrero-Gomez, E., Raducan, M., Echavarren, A.M. *Chem. Eur. J.* **2006**, *12*, 1677-1693.



Entry	Catalyst	Reaction time	Yields
1	147 , R = tBu	3 h	70%
2	153	3 h	80%
3	151	30 min	73%
4	152	30 min	76%

Table 8 Methoxycyclization of 1,6-Enyne 154

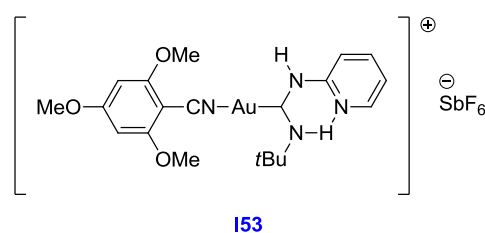


Figure 1 Gold-Complex used as Catalyst for Skeletal the Methoxycyclization of 1,6-Enyne 154

Thus, HBHC gold carbenes were shown to be highly active and good catalysts for the skeletal rearrangement and methoxycyclization of 1,6-enynes. Worthy of note, the steric and electronic properties of the amine chosen for the nucleophilic attack onto the gold-coordinated isocyanide induce substantial changes in both the catalytic activity of the complexes (higher yields for bulkier R substituents) and the selectivity of the reaction.

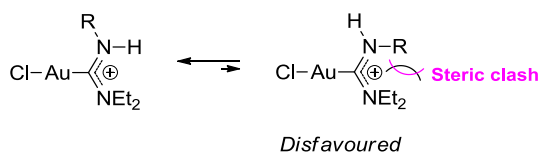
It is worth mentioning that the intramolecular hydrogen bond is split in the presence of MeOH. Hence, active catalysts are open carbene complexes (nitrogen acyclic carbene) in this particular case.

VII. Nitrogen Acyclic Gold(I) Carbenes

The observation that HBHCs efficiently catalyse the alkoxylation of 1,6-enynes led to the preparation of a series of NAC gold(I) complexes of Nitrogen Acyclic Carbenes (NACs) of the type $[AuCl\{C(NHR)(NHR')\}]$ or $[AuCl\{C(NHR)(NR_2)\}]$.¹⁰⁸ The carbene C-N bond shows a considerable multiple character, which results in an important restriction to rotation and thus the formation of stereoisomers. As long as carbenes from secondary amines are concerned, two stereoisomers are possible, among which one is clearly disfavoured for steric reasons (*Scheme*

¹⁰⁸ Bartolomé, C., Ramiro, Z., Garcia-Cuadrado, D., Pérez-Galan, P., Raducan, M., Bour, C., Echavarren, A.M., Espinet, P. *Organometallics* **2010**, 29, 951-956.

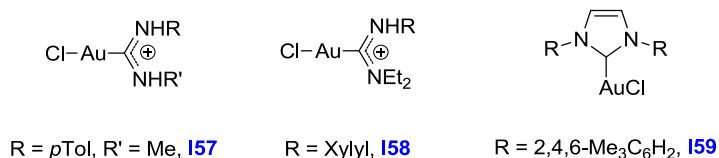
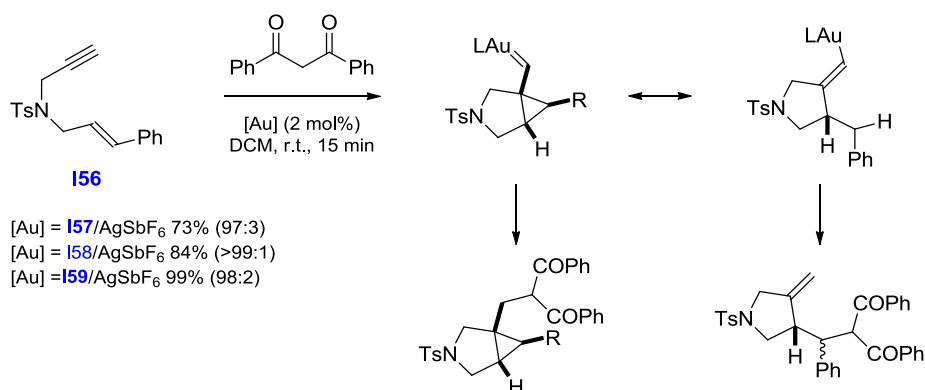
54). When it comes to complexes formed from primary amines, up to four stereoisomers are possible, the most favoured of which is often difficult to predict.



Scheme 54 Possible Stereoisomers for the NAC Complexes formed from NHEt_2

Most NAC-Au(I) complexes were overall at least as reactive and selective as the previously reported carbene-Au(I) complexes in the gold-catalyzed skeletal rearrangement and methoxycyclization of 1,6-enynes. In addition, these complexes have been successfully applied to the phenol synthesis, hydration of alkynes,¹⁰⁹ and synthesis of cage-like structures *via* the gold-catalyzed tandem reactions of diyne-diols and external nucleophiles.¹¹⁰

The site selectivity of the new gold(I) complexes was probed in the reaction of 1,6-enynes with dibenzoylmethane. The site of nucleophilic attack depends on the nature of the L ligand and reflects the carbenic or carbocationic character of the intermediates involved. As it happens, NAC leads to cyclization of enynes through intermediates that show a significant gold-carbene character, thus reflecting the highly electron-donating character of these ligands.



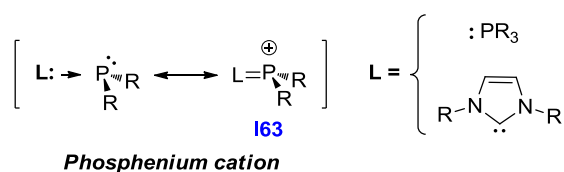
Scheme 55 Reaction of 1,6-Enyne **156** with Dibenzoylmethane

VIII. Cyclopropenyliidene-Stabilized Phosphenium Cations

¹⁰⁹ Hashmi, A.S.K., Hengst, T., Lothscütz, C., Rominger, F. *Adv. Synth. Catal.* **2010**, 352, 1315-1337.

¹¹⁰ Hashmi, A.S.K., Bührle, M., Wölfle, M., Rudolph, M., Wietek, M., Rominger, F., Frey, W. *Chem. Eur. J.* **2010**, 16, 9846-9854.

Phosphenium cations are compounds of formula $[R_2P:]^+$ which are isolobal with singlet carbenes and thus can be stabilized by electron donation into their empty orbital,¹¹¹ either by embedding the phosphorus into a heterocyclic scaffold¹¹² or by coordination to a Lewis base (Scheme 56).¹¹³ The presence of a lone pair of electrons on the phosphorus atom makes possible the use of the resulting adducts as ligands. Those are nonetheless poor σ -donors and strong π -acceptors. Especially when the Lewis base is a phosphine, the ground-state structure is dominated by the resonance form **163** which disfavours the formation of transition metal complexes. Even when the Lewis base is a NHC, the resulting ligand is strongly π -accepting.



Scheme 56 Conceivable Resonance Extremes of the Phosphenium-Base Adducts

Consequently, Alcarazo *et al.* the stabilization of phosphenium cations by the 1,2-bis(diisopropylamino)cyclopropenyl-3-ylidene moiety as a stronger σ -donor and even poorer π -acceptor than NHCs (Scheme 57).¹¹⁴ Cyclopropenylylidene-stabilized phosphenium cations can be prepared on a multigram scale in good to excellent yields by direct condensation of the chlorocyclopropenium salt¹¹⁵ with a range of secondary phosphines, and subsequent anion exchange.¹¹⁶

¹¹¹ For general reviews on the synthesis and structure of phosphenium cations, see: Cowley, A.H., Kemp, R.A. *Chem. Rev.* **1985**, *85*, 367-382; Gudat, D. *Chem. Rev.* **1997**, *163*, 71-106.

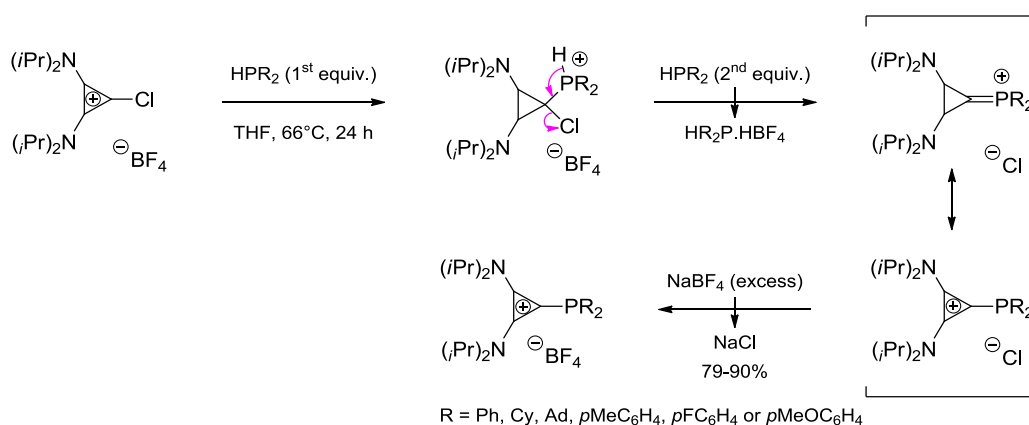
¹¹² The stabilization of phosphenium cations inside a carbocyclic system has also been achieved: Schmidpeter, A., Thiele, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 308-310. For the synthesis and reactivity of N-heterocyclic phosphenium cations, see for example: Denk, M.K., Gupta, S., Lough, A.J. *Eur. J. Inorg. Chem.* **1999**, 44-49; Caputo, C.A., Price, J.T., Jennings, M.C., MacDonald, R., Jones, N.D. *Dalton Trans* **2008**, 3461-3469; Gudat, D. *Acc. Chem. Res.* **2010**, *43*, 1307-1316.

¹¹³ For adducts with phosphines, see: Burford, N., Ragogna, P.J., MacDonald, R., Ferguson, M.J. *J. Am. Chem. Soc.* **2003**, *125*, 14404-14410; Burford, N., Ragogna, P.J. *J. Chem. Soc. Dalton Trans.* **2002**, 4307-4315; Burford, N., Ragogna, P.J., Sharp, K., MacDonald, R., Ferguson, M.J. *Inorg. Chem.* **2005**, *44*, 9453-9460. For adducts with pyridine derivatives and other N-based ligands, see: Burford, N., Losier, P., Phillips, A.D., Ragogna, P.J., Cameron, T.S. *Inorg. Chem.* **2003**, *42*, 1087-1091. For adducts with NHCs, see: Kuhn, N., Fahl, J., Bläser, D., Boese, R. *Z. Anorg. Allg. Chem.* **1999**, *625*, 729-734; Azani, M., Andrieu, J., Picquet, M., Richard, P., Hanquet, B., Tkatchenko, I. *Eur. J. Inorg. Chem.* **2007**, 4877-4883.

¹¹⁴ Lavallo, V., Canac, Y., Donnadiou, B., Schoeller, W.W., Bertrand, G. *Science* **2006**, *312*, 722-724; Schoeller, W.W., Frey, G., Bertrand, G. *Chem. Eur. J.* **2008**, *14*, 4711-4718. For the employment of this carbene to stabilize N^I and P^I centers, see: Bruns, H., Patil, M., Carreras, J., Vazquez, A., Thiel, W., Goddard, R., Alcarazo, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3680-3683; Back, O., Kuchenbeiser, G., Donnadiou, B., Bertrand, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 5530-5533.

¹¹⁵ Weiss, R., Wagner, K.G., Priesner, C., Macheleid, J. *J. Am. Chem. Soc.* **1985**, *107*, 4491-4499; A tungsten complex containing a cyclopropenylylidene-stabilized phosphenium cation has been described, although a different synthetic protocol was used, see: Huy, N.H.T., Donnadiou, B., Bertrand, G., Mathey, F. *Chem. Asian J.* **2009**, *4*, 1225-1228.

¹¹⁶ Petuskova, J., Bruns, H., Alcarazo, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 3799-3802.



Scheme 57 Synthesis of Cyclopropenylylidene-Stabilized Phosphenium Cations

The C-P bond length between the cyclopropenylylidene moiety is significantly shorter than typical C-P double bonds,¹¹⁷ which is indicative of marginal back donation from the phosphorus atom to the cyclopropenyl ring. According to electrochemical measurements and the analysis of the CO stretching frequencies for the corresponding rhodium complexes, the new phosphenium adducts have a slightly better donor capacity than triphenylphosphine, in spite of the cationic character of the phosphorus atom (*Table 9*).

Entry	Ligand	R	ν_{CO} (cm ⁻¹) [RhCl(CO)L ₂ (BF ₄) ₂]	$E_{1/2}$ ¹¹⁸
1		Ph	1971	0.955
2		Cy	1968	0.911
3		<i>p</i> -MeOC ₆ H ₄	1969	-
4		<i>p</i> -FC ₆ H ₄	1976	0.964
5		<i>p</i> -MeC ₆ H ₄	1969	0.915
6	(MeO) ₃ P	-	2011 ¹¹⁹	-
7	Ph ₃ P	-	1979 ¹⁰⁴	0.955
8	Cy ₃ P	-	1943 ¹⁰⁴	0.917

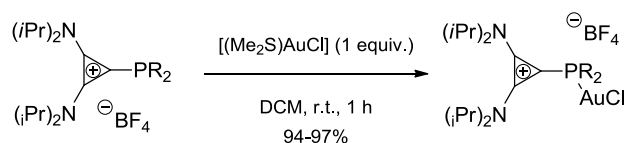
Table 9 Carbonyl stretching Frequencies in Complexes [RhCl(CO)L₂](BF₄)₂ in the solid State and electrochemical redox Potential of the corresponding Complexes [RhCl(cod)L](BF₄)

A set of gold complexes was prepared by addition of [(Me₂S)AuCl] to solutions of phosphenium adducts in dichloromethane (*Scheme 58*).

¹¹⁷ The carbon-phosphorous distance in an unstabilized ylide such as methylenetriphenylphosphorane (Ph₃P=CH₂) is 1.662(8) Å, see: Bart, J.C.J., *J. Chem. Soc. B* **1969**, 350-365.

¹¹⁸ Calibrated versus ferrocene/ferrocenium ($E_{1/2} = 0.46$ V), Bu₄NPF₆ (0.1 M) in DCM.

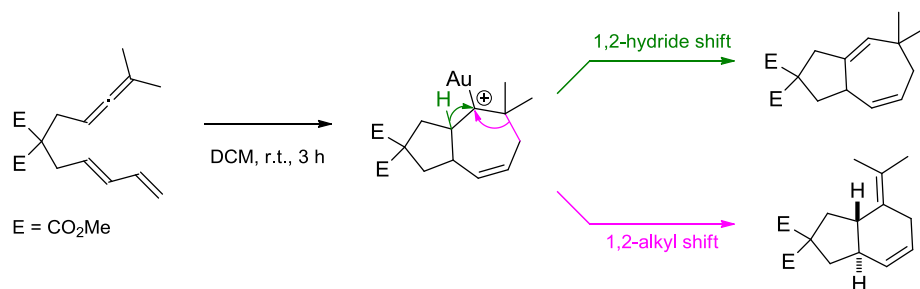
¹¹⁹ Azouri, M., Andrieu, J., Picquet, M., Cattet, H. *Inorg. Chem.* **2009**, 48, 1236-1242.



160, R = Ph, Cy or Ad

Scheme 58 Synthesis of Gold Complexes of Cyclopropenylylidene Phosphenium Cations

The catalytic performance of these compounds was compared to that of standard gold(I) phosphine complexes in various transformations. For example, the reaction of allenediene (*Table 10*). When π -acidic ligands L are used, the carbocationic nature of intermediate is enhanced, thus promoting ring contraction by a 1,2-alkyl shift. In contrast, strongly σ -donating ligands at the gold centre increase the carbene character, thus favoring the 1,2-hydride migration process. As illustrated in *Table 10*, the selectivity obtained using catalyst **160** (R = Ph) is comparable to that of phosphines, thus confirming the conclusions drawn from the spectroscopic and electrochemical measurements.



Entry	Conditions	L	Yields	Ratios
1	[LAuCl]/AgBF ₄ (2 mol%)	Ph ₃ P	75%	75:25
2		(PhO) ₃ P	98%	97:3
3	[LAuNTf ₂] (2 mol%)	160 , R = Ph	92%	87:13
4		IMes	95%	1:99

Table 10 Comparison of the Selectivity of different Ligands in the Gold-catalyzed Cyclization of Allenediene

The general utility of the catalysts was further demonstrated in other gold(I)-promoted processes such as the cycloisomerization of enynes,¹²⁰ the generation of pyrrolo[1,2-*a*]quinoline from *ortho*-alkynylated phenylpyrrole,¹²¹ the cyclopropanation of styrene,¹²² and an

¹²⁰ Trost, B.M., Trost, M.K. *J. Am. Chem. Soc.* **1991**, *113*, 1850-1852 ; Fürstner, J., Mlynarski, J., Albert, M. *J. Am. Chem. Soc.* **2001**, *123*, 11863-11869.

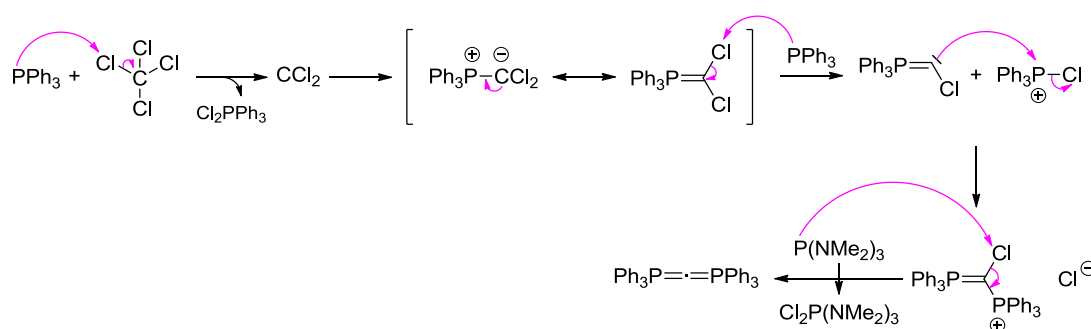
¹²¹ Mamane, V., Hannen, P., Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 4556-4575.

¹²² Johansson, M.J., Gorin, D.J., Staben, S.T., Toste, F.D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.

unprecedented hydroxide abstraction from a dibenzylic alcohol.¹²³ Interestingly, one can take advantage of the cationic nature of those ligands in recycling of the gold catalyst.

IX. Carbodiphosphanes

In the presence of excess PPh₃, the coordination of CCl₂ to the Lewis base leads to the formation of an adduct, to which the successive nucleophilic additions of PPh₃ and tris(dimethylamino)phosphane affords carbodiphosphorane C(PPh₃)₂ (Scheme 59).¹²⁴



Scheme 59 Synthesis of Carbodiphosphorane C(PPh₃)₂

Carbodiphosphanes feature a carbon(0) with two lone pairs of electrons, and thus can bear two metals, as demonstrated with the synthesis of [(AuMe)₂{μ-C(PMe₃)₂}] and [(AuMe){μ-C(PMe₃)₂}] reported by Schmidbaur in 1976 by mixing the ligand in THF with 1 or 2 equivalent(s) of AuCl(tht), respectively.¹²⁵ According to the calculated percent buried volumes (%V_{bur}),¹²⁶ C(PPh₃)₂ (%V_{bur} of 44.7¹²⁷) would surround the metal almost as much as IPr.¹¹⁴ Comparatively, the %V_{bur} of the dinuclear complex is lower (%V_{bur} of 41.3) owing to the intrinsically more acute PCP angle. Yet, the free space of the sphere is occupied by two gold atoms in this case.¹²⁸

¹²³ For a related transformation, see: Cordier, P., Aubert, C., Malacria, M., Lacôte, E., Gandon, V. *Angew. Chem. Int. Ed.* **2009**, *48*, 8757-8760.

¹²⁴ El-Hallani, A., Bour, C., Gandon, V. *Adv. Synth. Catal.* **2011**, *353*, 1865-1870. For the preparation of hexaphenylcarbodiphosphorane, see: Appel, R., Knoll, F., Schöllner, H., Wihler, H.-D. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 702.

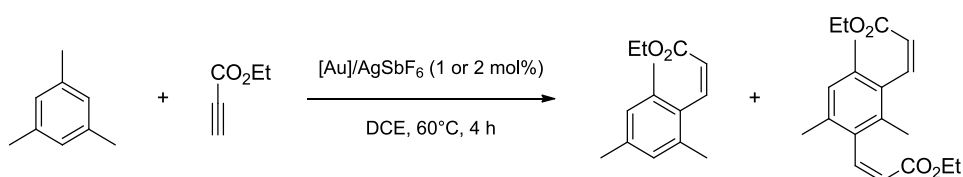
¹²⁵ Schmidbaur, H., Gasser, O. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 502; Schmidbaur, H., Zybilla, C.E., Müller, G., Krüger, C. *Angew. Chem. Int. Ed. Engl.* **1993**, *22*, 729. For the preparation of [AuCl{C(PPh₃)₂}] and [(AuCl)₂{μ-C(PPh₃)₂}], see: Vincente, J., Singhal, A.R., Jones, P.G. *Organometallics* **2002**, *21*, 5887.

¹²⁶ Poater, A., Cosenza, B., Correa, A., Giudice, S., Ragone, F., Scarano, V., Cavallo, L. *Eur. J. Inorg. Chem.* **2009**, 1759; Clavier, H., Nolan, S.P. *Chem. Commun.* **2010**, *46*, 841.

¹²⁷ This value was obtained from the optimized geometry of [AuCl{C(PPh₃)₂}] at the M06/LACVP** level of theory. Using the coordinates of the X-ray structure of [H₃B{C(PPh₃)₂}] (see: Petz, W., Oxler, F., Neumüller, B., Tonner, R., Frenking, G. *Eur. J. Inorg. Chem.* **2008**, 4507), a %V_{bur} of 46.6 was obtained.

¹²⁸ This value was obtained from the optimized geometry of [(AuCl)₂{μ-C(PPh₃)₂}] at the M06/LACVP** level of theory. Using the coordinates of the X-ray structure (see ref. **113**), a %V_{bur} of 42.0 was obtained.

To evaluate the donor ability of carbodiphosporanes, the selectivity of the mono- and dinuclear complexes was compared to that of $(\text{AuCl}\{\text{P}[\text{O}-(2,4-(t\text{Bu})_2\text{C}_6\text{H}_3)_3]\})$, $[\text{AuCl}(\text{PPh}_3)]$ and $[\text{AuCl}(\text{IPr})]$ as prototypes of phosphite, phosphine and carbene gold complexes. More specifically, their carbophilicity was tested in the hydroarylation of ethyl propiolate by mesitylene (Table 11).¹²⁹ Kinetically speaking, the dinuclear catalyst outperformed the others. The reaction was slowed down, however, when the mononuclear catalyst was used. This was rationalized in that an electron-poor alkyne is used, so that the most basic ligands favour the reaction¹³⁰ (as illustrated in the original paper) but the σ -donation is funnelled toward only one gold centre in the mononuclear complex, which would result in excessive electron enrichment for the initial activation of the alkyne to be efficient in this particular case.



Entry	[Au]	Yields	Ratios
1	$[\text{AuCl}(\text{PPh}_3)]$	78%	96/4
2	$[\text{AuCl}(\text{IPr})]$	81%	98/2
3	$[\text{AuCl}\{\text{C}(\text{PPh}_3)_2\}]$	30%	90/10
4	$[(\text{AuCl})_2\{\mu\text{-C}(\text{PPh}_3)_2\}]$	Quant.	95/5

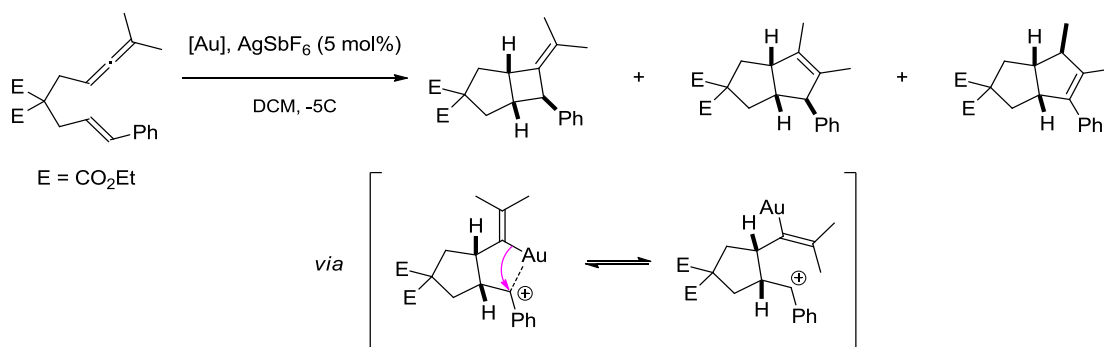
Table 11 Hydroarylation of Ethyl Propiolate by Mesitylene

Conversely, the selectivity for the [2+2] cycloadduct in the cycloisomerization of eneallene is much higher with the monogold complex (Table 12). In this type of transformation, it was shown that the ancillary ligand exerts a dramatic influence on the outcome.¹³¹ The ratio of the [2+2] cycloadduct increases as the metal becomes more electron rich, which could be explained by a better stabilization of the carbocationic centre of the vinylgold intermediate, leading to direct vinylation.

¹²⁹ Reetz, M.T., Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485.

¹³⁰ One cannot exclude the participation of the two gold atoms in the activation of the substrate; Cheong, P. H.-Y., Morganelli, P., Luzung, M.R., Houk, K.N., Toste, F.D. *J. Am. Chem. Soc.* **2008**, *130*, 4517; Weber, D., Tarselli, M.A., Gagné, M.R. *Angew. Chem. Int. Ed.* **2009**, *48*, 5733; Weber, D., Gagné, M.R. *Org. Lett.* **2009**, *11*, 4962; Odabachian, Y., Le Goff, X.-F., Gagosz, F. *Chem. Eur. J.* **2009**, *15*, 8966; Seidel, G., Lehmann, C.W., Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 8466; Schmidbaur, H., Schier, A. *Organometallics* **2010**, *29*, 2.

¹³¹ Alcarazo, M., Stork, T., Anoop, A., Thiel, W., Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2542; Luzung, M.R., Maulen, P., Toste, F.D. *J. Am. Chem. Soc.* **2007**, *129*, 12402; Teller, H., Flüge, S., Goddard, R., Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 1949.



Entry	[Au]	Yields	Ratios
1	[AuClP(OAr) ₃]	82%	1:1.6:1
2	[AuClPPh ₃]	85%	1.8:1.4:1
3	[AuCl(IPr)]	90%	3.9:1:1
4	[AuCl{C(PPh ₃) ₂ }]	90%	11.7:1:1.6
5	[(AuCl) ₂ {C(PPh ₃) ₂ }]	94%	2.9:1.2:1

Table 12 Cycloisomerization of Eneallene

The selectivities observed strongly suggest that hexaphenylcarbodiphosphorane can be used as a stronger electron-donor compared to NHCs. Because a dual activation mechanism can be the operative one in some transformations, however, the rationalization of the results obtained when C(PPh₃)₂ bears two gold atoms is less evident.

Present Work

Chapter I

Application of the Metal-Catalyzed Rearrangement of Propargyl Acetates to the Total Synthesis of Natural Products of the Neomerane Family

I. Introduction

In 1989, three new monobrominated sesquiterpene alcohols, among which the unprecedented (-)-Neomeranol **s1** (Figure 1), were isolated by Cardellina and co-workers from the calcareous green alga *Neomeris annulata* and reported to be responsible for the cytotoxicity and phytotoxicity observed in organic soluble extracts of this plant.¹³² Their structures were elucidated *via* the application of advanced 2D NMR techniques and the absolute configuration of (-)-Neomeranol determined by a modified Horeau's method, based on the kinetic resolution of racemic 2-phenylbutyryl chloride by the hindered chiral secondary alcohol.¹³³

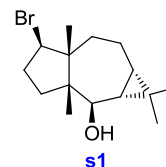
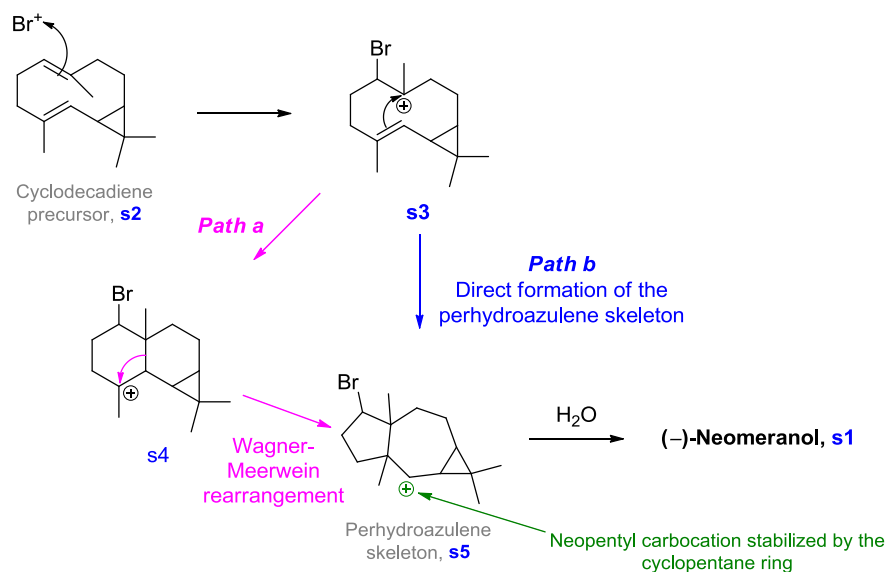


Figure 1 Chemical Structure of

The biosynthesis of (-)-Neomeranol was rationalized by the authors as possibly resulting from the bromonium ion induced cyclization of a cyclodecadiene precursor **s2** (Scheme 60). The carbocation so formed would then either rearrange prior to the nucleophilic addition of water (Scheme 60, Path a) or directly lead to the formation of the perhydroazulene skeleton **s5** (Scheme 60, Path b), with the neopentyl carbocation being stabilized by the cyclopropane ring.

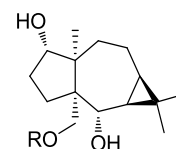
¹³² Zetker, A.S., Martin, G.E., Barnekow, D.E., Cardellina, J.H. *J. Am. Chem. Soc.* **1989**, *111*, 3511-3517.

¹³³ Barnekow, D.E., Cardellina, J.H. *Tetrahedron Lett.* **1989**, *30*, 3629-3632.



Scheme 60 Mechanism Proposal for the Biosynthesis of (-)-Neomeranol

Other neomerane-type sesquiterpenoids were isolated in 2014 by Zhang and co-workers from the roots of *Valeriana officinalis* var. *latifolia*, a variety of grass largely distributed in mainland China.¹³⁴ The structures of the latter compounds were elucidated by spectroscopic analysis. Among them, (+)-Valeneomerin B **s6** (Figure 2, R = COCH₃) exhibits significant neuroprotective effects against H₂O₂ induced oxidative stress and has a carbon skeleton closely related to that of (-)-Neomeranol. Its absolute configuration was determined by X-ray crystallographic analysis of its hydrolysis derivative **s7** (Figure 2, R = H).



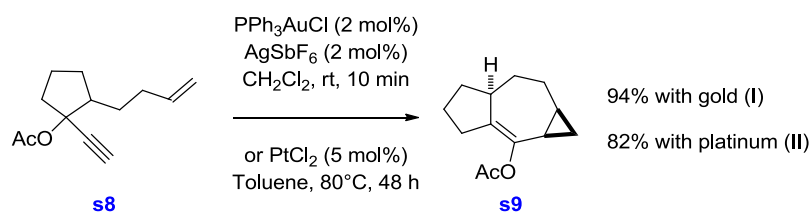
R = COCH₃ (+)-Valeneomerin B, **s6**
R = H, **s7**

Figure 2 Chemical Structures of (+)-Valeneomerin B and its Hydrolysis Derivative

None of Neomeranol and Valeneomerin B natural products has been synthesized to date. However, a new entry to the synthesis of complex polycyclic structures and fused cyclopropane derivatives has been provided by the metal-catalyzed rearrangement of propargyl acetates. More specifically, in 2008, the tricyclic core of (±)-Neomeranol and (±)-Valeneomerin B was obtained in excellent yields either under gold or platinum catalysis (Scheme 61).¹³⁵

¹³⁴ Han, Z.-Z., Zu, X.-P., Wang, J.-X., Li, H.-L., Chen, B.-Y., Liu, Q.-X., Hu, X.-Q., Yan, Z.-H., Zhang, W.-D. *Tetrahedron* **2014**, *70*, 962-966.

¹³⁵ Moreau, X., Goddard, J.-P., Bernard, M., Lemièrre, G., López-Romero, J.M., Mainetti, E., Marion, N., Mouriès, V., Thorimbert, S., Fensterbank, L., Malacria, M. *Adv. Synth. Catal.* **2008**, *350*, 43-48.



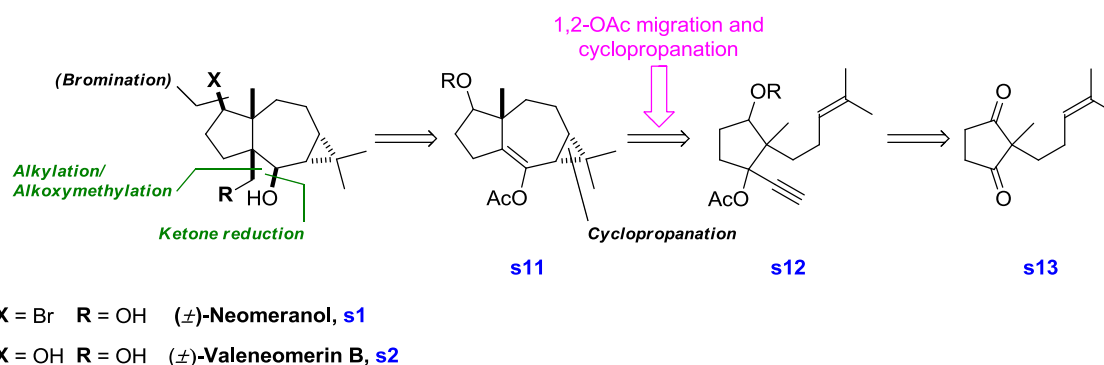
Scheme 61 Formation of the Tricyclic Core of (±)-Neomeranol and (±)-Valeneomerin B under Gold or Platinum Catalysis

In this context, our goal was to apply the metal-catalyzed rearrangement of propargyl acetates to the total synthesis of (±)-Neomeranol and (±)-Valeneomerin B.

II. Preparation of the Common Intermediate to (±)-Neomeranol and (±)-Valeneomerin B

1. Retrosynthetic Analysis of (±)-Neomeranol and (±)-Valeneomerin B

From a retrosynthetic point of view, both (±)-Neomeranol and (±)-Valeneomerin B could potentially be obtained after alkylation/alkoxymethylation followed by ketone reduction of a common tricyclic intermediate **s11** resulting from the rearrangement of a propargyl acetate precursor **s12** and subsequent intramolecular cyclopropanation (Scheme 62). The propargyl acetate derivative **s12** would come from the desymmetrization of the corresponding 1,3-dione **s13**.

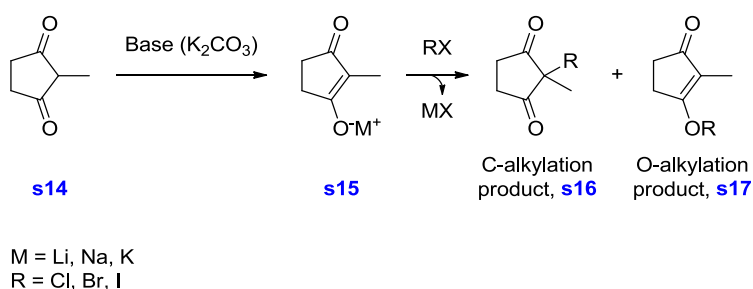


Scheme 62 Retrosynthetic Analysis of (±)-Neomeranol and (±)-Valeneomerin B

2. Retrosynthetic Analysis of the 1,3-dione **s13**

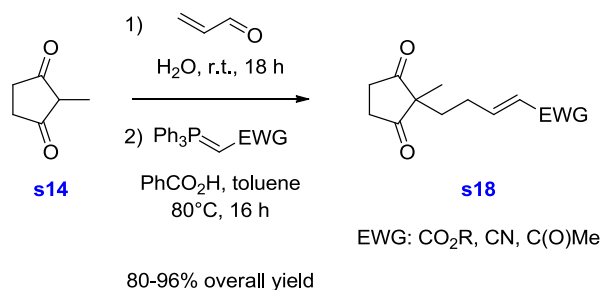
a) Alkylation of 2-methyl-cyclopentan-1,3-dione

Preparation of the starting 1,3-dione **s13** by the simple alkylation of the commercially available 2-methyl-cyclopentan-1,3-dione (*Scheme 63*, **s14**) was envisioned. However, it has been shown by Schick and co-workers that the regioselectivity of the alkylation of alkali metal salts of 2-methyl-cyclopentan-1,3-dione **s15** with alkyl halides significantly depends on the structure of the alkylating reagent and the type of solvent used in the reaction. More specifically, C-alkylation is the major pathway with MeI, allyl and propargyl bromides, and benzyl chloride as the electrophile only. Moreover, polar aprotic solvents like DMF, DMSO, HMPT or acetonitrile favour O-alkylation whereas water favours C-alkylation.¹³⁶



Scheme 63 Regioselectivity Issue Encountered in the Alkylation of 2-methylcyclopentan-1,3-dione

Yet, Riant and co-workers reported in 2012 that the treatment of 2-methylalkan-1,3-diones by acrolein in water gives quantitatively the corresponding aldehydes, which can further be used in a Wittig reaction (*Scheme 64*).¹³⁷



Scheme 64 Regioselective Alkylation of 2-methylcycloalkan-1,3-diones with Acrolein

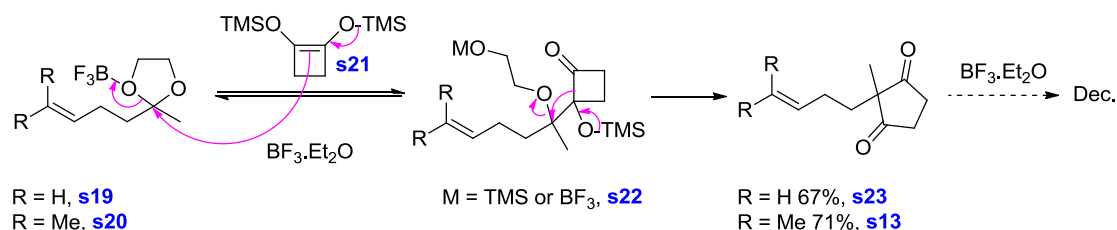
b) BF₃-mediated Pinacol ring Enlarging Annulation

Alternatively, the 1,3-dione **s13** could be prepared according to a method reported by Curran in 1995, which consists in the BF₃-mediated pinacol ring enlarging annulation reaction of an alkenyl acetal (*Scheme 65*, **s19** or **s20**) in the presence of 1,2-bis(trimethylsilyl)aclyoin **s21** (*Scheme 65*). The reaction was initially reported with alkynyl acetals but alkenyl

¹³⁶ Schwarz, H., Finger, A., Schick, H. *Tetrahedron* **1982**, 38, 1279-1283.

¹³⁷ Deschamp, J., Hermant, T., Riant, O. *Tetrahedron* **2012**, 68, 3457-3467.

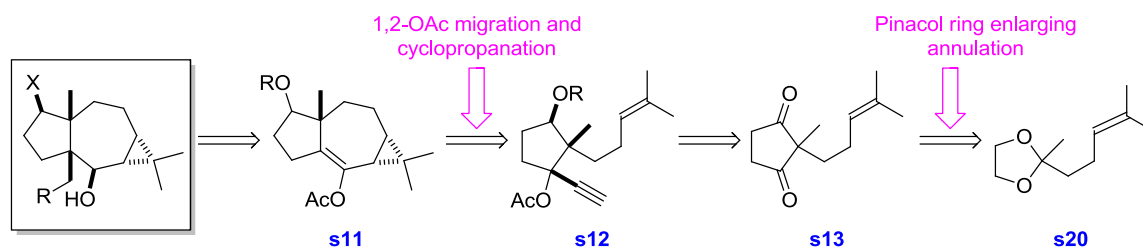
cyclopentanedione cyclizations were also shown to proceed smoothly. A careful control of the reaction temperature and time was however required in the latter case, since extended exposure of alkenyl acetals **s19** and **s20** to $\text{BF}_3 \cdot \text{Et}_2\text{O}$ without any nucleophile resulted in complete decomposition (*Scheme 65*).¹³⁸



Scheme 65 Alkenyl Cyclopentanedione Ring Enlarging Annulations

3. Global Retrosynthetic Scheme

Because of the toxicity of acrolein, the latter strategy was selected for the preparation of the 1,3-dione **s13**, so that the global retrosynthetic scheme of (\pm)-Neomeranol and (\pm)-Valeneomerin B was the following (*Scheme 66*).



X = Br R = OH (\pm)-Neomeranol, **s1**

X = OH R = OH (\pm)-Valeneomerin B, **s2**

Scheme 66 Global Retrosynthetic Scheme of (\pm)-Neomeranol and (\pm)-Valeneomerin B

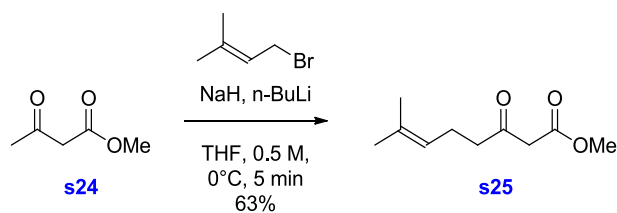
4. Preparation of the 1,3-dione **s13**

a) Synthesis of the Starting Acetal **s20**

The acetal to be engaged into the 1,3-dione formation step is commercially available but expensive,¹³⁹ so that it was synthesized in three steps from methyl acetoacetate **s24**. Successive deprotonation with NaH and *n*-BuLi afforded the corresponding bis-anion, to which 1-bromo-3-methyl-2-butene was added to give the allylated product **s25** in moderate yields (*Scheme 67*).

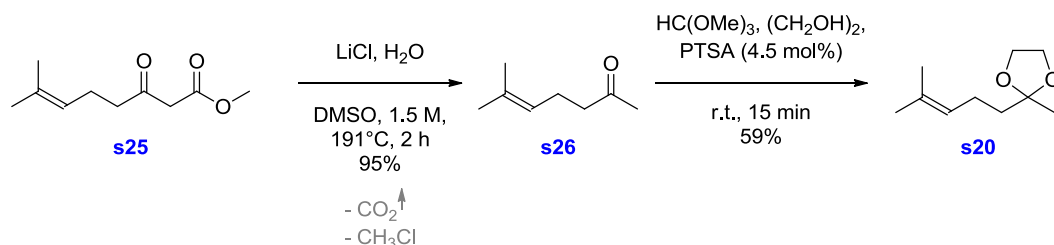
¹³⁸ Balog, A., Curran, D.P. *J. Org. Chem.* **1995**, *60*, 337-344; Balog, A., Geib, S.J., Curran, D.P. *J. Org. Chem.* **1995**, *60*, 345-352.

¹³⁹ Sigma Aldrich: 250 mg costs 119.00 €.



Scheme 67 Alkylation of Methyl Acetoacetate s24

The decarboxylation of the resulting ketoester **s25** was performed under Krapcho conditions. Finally, the acetal **s20** was formed using 4.5 mol% of *p*-toluenesulfonic acid (PTSA) with ethylene glycol as the solvent (*Scheme 68*). Overall, the starting acetal **s20** was prepared in 35% yield over 3 steps on the 100 mmol-scale.

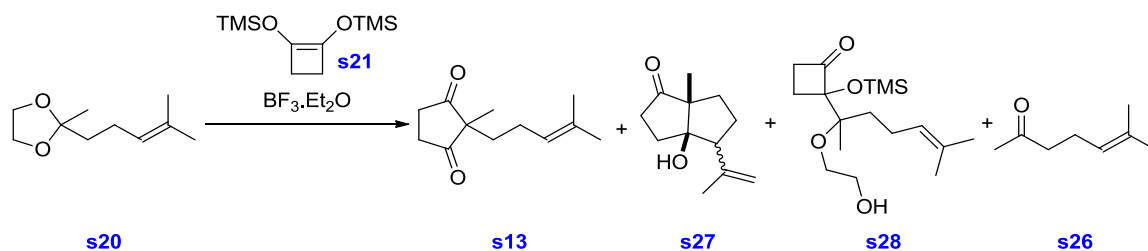


Scheme 68 Krapcho Decarboxylation of s25 and Formation of the Acetal s20

b) Studies toward the BF₃·Et₂O-mediated Pinacol Ring Enlarging Annulation

The acetal **s20** was reacted with the commercially available 1,2-bis(trimethylsilyl)acyloin **s21** in the conditions described by Curran. Unfortunately, and in sharp contrast to Curran's report, very low yields and reproducibility issues were encountered. It was eventually found that exposure of the expected 1,3-dione **s13** to the reaction conditions for more than an hour actually results in further Prins intramolecular cyclization (*Table 13, entry 1*). Indeed, a very large excess of BF₃·Et₂O was used (10 equiv.), so that the Lewis-acid activation of one ketone and addition of the highly nucleophilic prenyl function may occur.

Following further time and temperature investigations, the best conditions were found to be those where the temperature was increased from -78 to -50°C over 30 minutes and the reaction quenched at the latter temperature with water (*Table 13, entry 2*). Yet, the yield remained much lower than expected (38% vs. 71% reported in the literature). What is more, scaling-up the reaction resulted in a drastic alteration of the yield (*Table 13, entry 3*).



Entry	Scale	C	Reaction temperature and time	Neq $\text{BF}_3 \cdot \text{Et}_2\text{O}$	Isolated Yields
1	1 mmol	0.2 M	-78°C for 30 min then -78°C → -10°C over 2.5 h	10	35% s13 + 19% s27
2	1 mmol	0.2 M	-78°C → -50°C over 30 min	10	38% s13
3	10 mmol	0.2 M	-78°C → -50°C over 30 min	10	15% s13
4	1 mmol	0.2 M	-78°C for 10 min	10	100% s26
5	1 mmol	0.2 M	-78°C → -50°C over 30 min	5	9% s13 + 22% s28
6	1 mmol	0.1 M	r.t. for 2.5 h	1	12% s13

Table 13 Selection of some of the Conditions Tested for the Pinacol Ring Enlarging Annulation

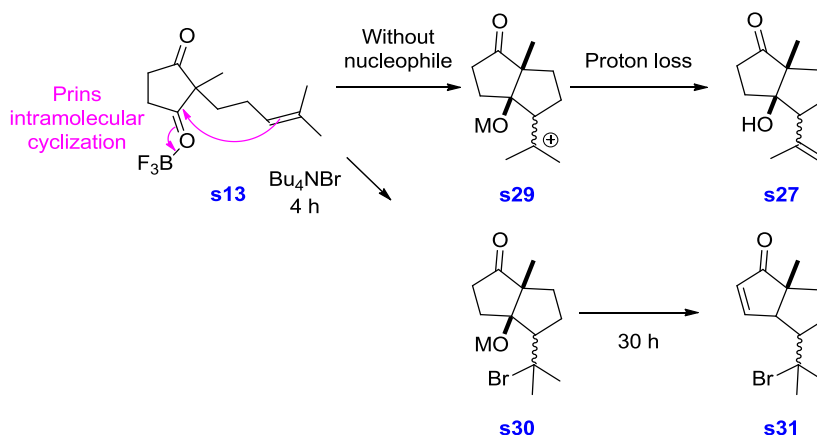
Shorter reaction times led to the recovery of the initial ketone (Table 13, entry 4), which means that either no reaction occurred or the cyclobutanone intermediate **s22** was formed but reversed to the starting material (see Scheme 65), as previously reported by Burnell and co-workers,¹⁴⁰. The acetal **s20** is presumably hydrolyzed in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and water during the work-up.

Burnell reported some examples where the reaction was performed in two steps, from either the ketone or the acetal as the starting material. In that event, the cyclobutanone intermediate **s22** is formed preliminary to the addition of excess $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or amberlyst 15.¹⁴¹ Unfortunately, none of the two-step-procedures tested could be successfully employed in the formation of the desired 1,3-dione **s13** (Table 13, entries 5-6). Actually, **s13** was already formed upon the addition of 1 equivalent of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Table 13, entries 5-6), although the cyclobutanone compound **s28** could be isolated at some point (Table 13, entry 5). Further addition of a large excess of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was responsible for decomposition.

¹⁴⁰ Jenkins, T.J., Burnell, D.J. *J. Org. Chem.* **1994**, 59, 1485-1491.

¹⁴¹ Crane, S.N., Jenkins, T.J., Burnell, D.J. *J. Org. Chem.* **1997**, 62, 8722-8729; Crane, S.N., Jenkins, T.J., Burnell, D.J. *J. Org. Chem.* **1998**, 63, 1352-1355; Pottie, I.R., Crane, S.N., Gosse, A.L., Miller, D.O., Burnell, D.J. *Can. J. Chem.* **2010**, 88, 1118-1124.

Structures similar to **s27** were reported by Curran when the cyclization was performed in the presence of Bu_4NBr or Bu_4NI (Scheme 69, **s31**). Here, in the absence of a nucleophile in the reaction mixture, proton loss occurs instead (Scheme 69, upper part).



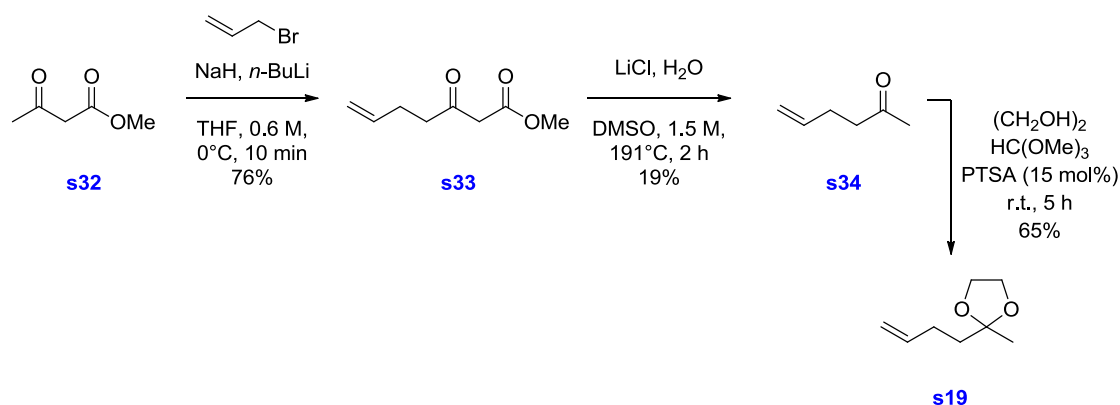
Scheme 69 Prins Intramolecular Cyclization of **s13** in the Presence of a Large Excess of $\text{BF}_3 \cdot \text{Et}_2\text{O}$

5. Modification of the Synthetic Scheme toward the 1,3-dione **s13**

To avoid the undesired Prins intramolecular cyclization of **s13** (Scheme 69), the synthetic scheme was modified so that the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -mediated ring enlarging annulation was now performed on an acetal precursor bearing a terminal alkene (see Scheme 71), the prenyl function being introduced post-cyclization *via* cross-metathesis with 2-methyl-2-butene (see Table 14).

a) Synthesis of Acetal **s19** Bearing a Terminal Alkene

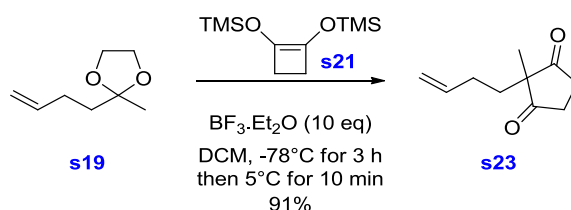
Acetal **s19** was prepared using very similar conditions as those previously employed in the synthesis of **s20** (Scheme 70). Ketone **s34** was nonetheless isolated in very poor yields, owing to its volatility. For this reason, and because large quantities of the acetal were required, the latter was prepared from the commercially available ketone.



Scheme 70 Synthesis of Acetal **s19** Bearing a Terminal Alkene

b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -mediated Pinacol Ring Enlarging Annulation from **s19**

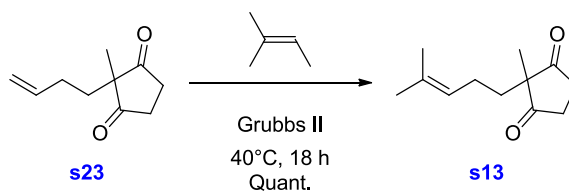
With a terminal alkene instead of a prenyl and on condition that both temperature and time are carefully controlled, excellent yields of the 1,3-dione **s23** were obtained (Scheme 71). The reaction could be performed on the 10 mmol-scale, so that multi-gram quantities of **s23** could be prepared. For good yields to be obtained, however, particularly crucial was the careful control of the temperature during the last 10 minutes of the reaction. Indeed, the further was the temperature from 5°C , the lower was the yield. Worthy of note, procedures with the initial ketone **s34** as the starting material were not successful.



Scheme 71 Formation of the 1,3-dione **s23** under the conditions reported by Curran

c) Cross-metathesis

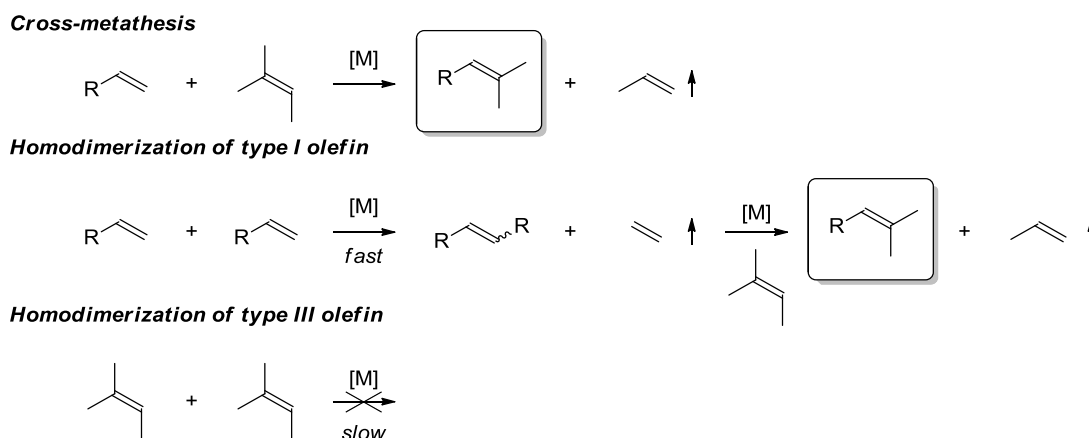
Cross-metathesis then revealed extremely efficient in introducing the prenyl moiety post-cyclization (Table 14). The reaction was very selective and, even on gram-scale (10 mmol-scale), excellent yields were obtained (Table 14, entry 1). Nevertheless, in order to perform the reaction on a multi-gram scale, the latter was further optimized so that the reaction was finally performed neat (in 2-methyl-2-butene as the solvent) and with a very low loading of Grubbs II catalyst (Table 14, entry 2). Scaling-up the reaction did not alter the yield, so that the 1,3 dione **s13** could be prepared on the 100 mmol-scale in 81% yield (Table 14, entry 3). No reaction occurred, however, when the Grubbs II catalyst was replaced with Grubbs I (Table 14, entry 4).



Entry	Scale (mmol)	Catalyst	Catalyst loading	Concentration	Yields
1	10	Grubbs II	7.5 mol%	18.2 mM in DCM	Quant.
2	1	Grubbs II	0.5 mol%	neat	87%
3	100	Grubbs II	0.5 mol%	neat	81%
4	0.1	Grubbs I	5 mol%	neat	No reaction

Table 14 Optimization of the Cross-metathesis Reaction between **s23** and 2-methyl-2-butene

The exclusive formation of the expected product **s13** can be rationalized on the basis of the model reported by Grubbs in 2003 to predict the selectivity and stereoselectivity in olefin cross-metathesis, in which several classes of olefins have been investigated and categorized by their relative abilities to undergo homodimerization, and the susceptibility of their homodimers toward secondary metathesis reactions.¹⁴² Basically, selective cross metathesis can be achieved when olefins from two different types are used due to their significantly different and/or slower rates of dimerization than the cross-metathesis product formation, for instance when an olefin of high reactivity is reacted with an olefin of lower reactivity (because of its steric bulk or its electron deficiency) (*Scheme 72*). Although one olefin may initially homodimerize, the homodimer so formed readily undergoes secondary metathesis with the olefin of lower reactivity (*Scheme 72, Homodimerization of type I olefin*). It is noteworthy that the inertia of the Grubbs I catalyst (Table 14, *entry 4*) is consistent with Grubbs' report that 1,1-disubstituted olefins homodimerize slowly in comparison to cross-metathesis (so that the former reaction does not occur) in the presence of the Grubbs II catalyst, while these olefins behave as spectators to cross-metathesis in the presence of the Grubbs I and Schrock catalysts.



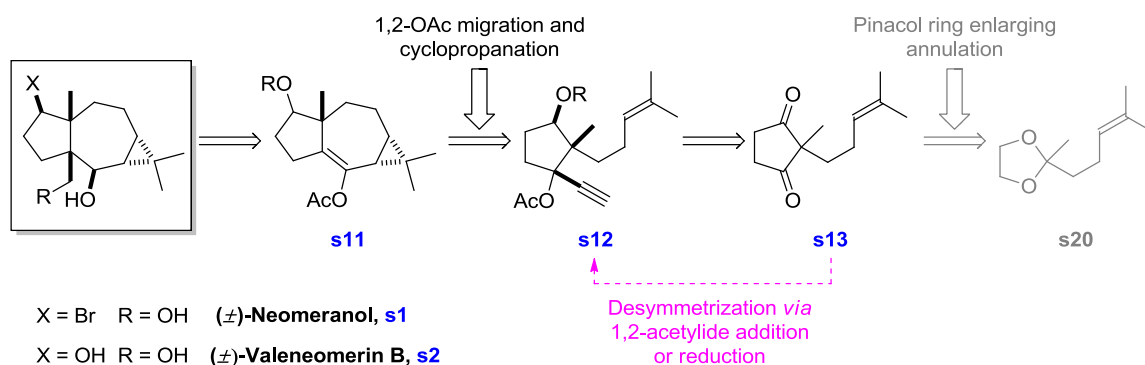
Scheme 72 Reactions in Cross metathesis of Type I and Type III Olefins

6. Synthesis of the Propargyl Acetate Precursor **s37**

a) *Desymmetrization of the 1,3-dione s13*

Two different strategies were to be envisioned for the desymmetrization of **s13**, considering either the introduction of the alkyne moiety present in the propargyl acetate precursor **s12**, or the monoreduction of the 1,3-dione (*Scheme 73*).

¹⁴² Chatterjee, A.K., Choi, T.-L., Sanders, D.P., Grubbs, R.H. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.

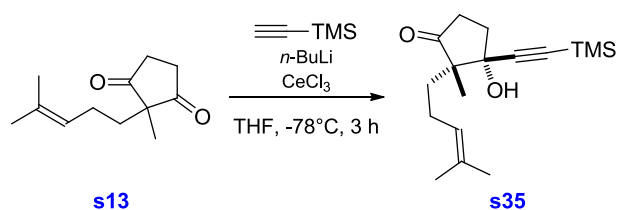


Scheme 73 Strategies Envisioned toward the Desymmetrization of **s13**

The former strategy was chosen (desymmetrization *via* 1,2-acetylide addition), for the following reasons.

- The stereogenic centre that would result from a 1,2-acetylide addition is not retained in the metal-catalyzed rearrangement step. Conversely, the stereogenic centre that would result from the monoreduction of **s13** remains in both (\pm)-Neomeranol and (\pm)-Valeneomerin B. Therefore, a good control over the diastereoselectivity of the reduction is required, which should be better achieved in a late stage of the synthesis.
- We were interested in exploring the reactivity of the cyclopentanone derivative **s37** of the propargyl acetate precursor **s12** in the key 1,2-OAc migration and cyclopropanation step.

Thus, the desymmetrization of **s13** *via* 1,2-acetylide addition was studied and, because Grignard reagents decompose rapidly, the use of the lithium salt of TMSA was considered at first over that of ethynylmagnesium bromide. Since TMSA is bigger, it might also induce a better diastereoselectivity. The lithium nucleophile was formed *via* the deprotonation of TMSA with *n*-BuLi. Unfortunately, this resulted in incomplete conversion and moderate yields of a 1:1 mixture of diastereomers (Table 15, entry 1).



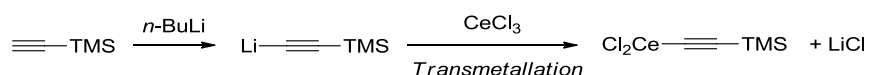
Entry	Scale	Nequiv. Nu ⁻	Nequiv. CeCl ₃	Temperature and reaction time	Conv.	Yields
1	0.3 mmol	1.2	-	-70°C, 1 h	81%	41%

2	0.5 mmol	2.4	-	-70°C, 1 h	90%	43%
3	0.5 mmol	3	3.5 eq	-78°C, 3 h	Total	69%
4	3 mmol	3	3.5 eq	-78°C, 3 h	Total	81%
5	15 mmol	3	3.0 eq	-78°C, 3 h	Total	95%

Table 15 Optimization of the Desymmetrization of **s13** via the 1,2-Addition of TMSA

Undesired deprotonation at the active methylene position might occur, so that twice more equivalents of *n*-BuLi were used. But the yield remained moderate, although the conversion was slightly improved (Table 15, entry 2).

Imamoto and co-workers demonstrated that in the presence of anhydrous cerium(III) chloride, organolithiums and Grignard reagents react with ketones to afford addition products in high yields, even with substrates susceptible to abnormal reactions such as enolization, reduction, condensation or conjugate addition. In the particular case of organolithiums, organocerium reagents (possessing a cerium-carbon σ -bond) may be generated *via* Li->Ce transmetallation, that would be less basic than organolithiums or Grignard reagents (Scheme 74).¹⁴³ Thus, the role of CeCl₃ would be dual in this case (Lewis activation of the carbonyl function and generation of an organocerium reagent *via* transmetallation with the organolithium). From a synthetic standpoint, the organocerium nucleophile is generated prior to the addition of the carbonyl compound to the reaction mixture.



Scheme 74 Generation of an Organocerium Nucleophile in the Presence of Anhydrous CeCl₃

The white crystals of the commercially available cerium(III) chloride heptahydrate are dried according to the procedure reported by Imamoto,¹⁴⁴ as follows. Cerium(III) chloride heptahydrate is evacuated to 0.1 mm. After gradual warming to 90°C with an oil bath, the flask is heated at 100°C for 3.5 h with intermittent shaking to give cerium(III) chloride monohydrate. The latter is then gradually warmed to 140°C under reduced pressure (0.1 mm) without stirring

¹⁴³ Imamoto, T., Takiyama, N., Nakamura, K. *Tetrahedron Lett.* **1985**, 26, 4763-4766; Imamoto, T., Takiyama, N., Nakamura, K., Hatajima, T., Kamiya, Y. *J. Am. Chem. Soc.* **1989**, 111, 4392-4398; Imamoto, T. *Pure and Appl. Chem.* **1990**, 62, 747-752. The identity and purity of the reagent written as CeCl₃/RLi is not well established: Evans, W.J., Feldman, J.D., Ziller, J.W. *J. Am. Chem. Soc.* **1996**, 118, 4581-4584.

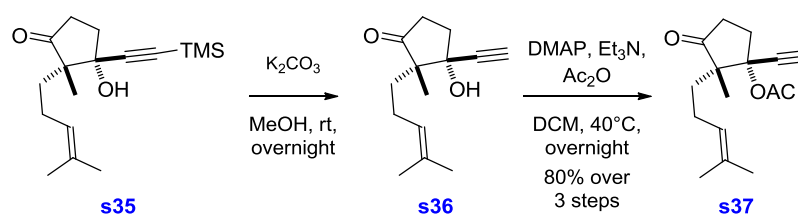
¹⁴⁴ Takeda, N., Imamoto, T. *Organic Syntheses* **2004**, 200, and references cited therein.

before heating at 150°C at 0.1 mm for 2 h with gentle stirring. anhydrous cerium(III) chloride is obtained as a fine, white powder.

The addition of anhydrous CeCl_3 to the reaction mixture gave total conversion toward a single diastereomer and considerably improved the yield (Table 15, entry 3). It is worth mentioning the necessity to precisely follow the above-mentioned drying procedure, since no reaction occurs otherwise.¹⁴⁵ To our delight, scaling-up the reaction afforded even better yields (Table 15, entries 4-5).

b) Deprotection and Acetylation

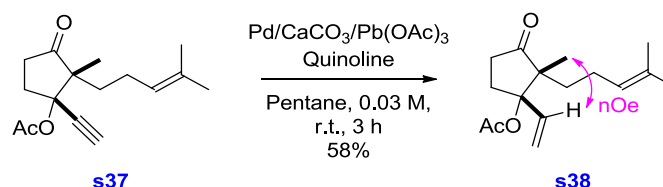
The deprotection of the alkyne was performed with K_2CO_3 in methanol (Scheme 75). The resulting tertiary alcohol is particularly hindered, so that reflux and a long reaction time were necessary for its acetylation to be complete. Overall, propargyl acetate **s37** was obtained in 80% yield over 3 steps.



Scheme 75 Deprotection of the Alkyne followed by Acetylation of the Tertiary Alcohol **s36**

c) Determination of the Diastereoselectivity of the 1,2-acetylide Addition

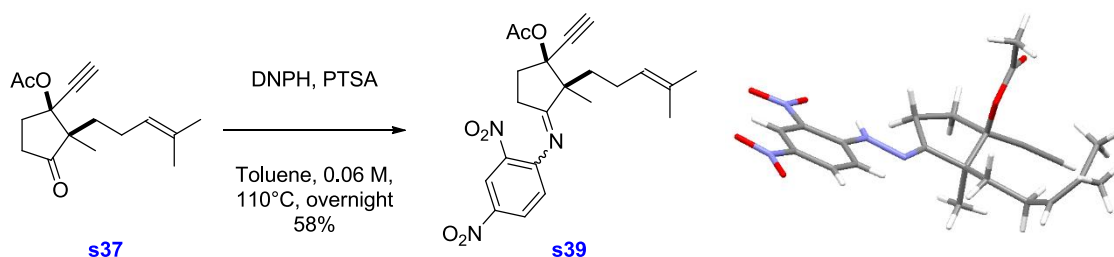
The diastereoselectivity of the desymmetrization was determined by the selective reduction of the alkyne moiety using Lindlar's catalyst (Scheme 76). A Noesy experiment was performed on the product **s38**, which showed a correlation between the internal proton of the alkene and the methyl group in α -position to the ketone, indicative of a *cis*-relationship between the alkyne and the methyl group in **s37**.



Scheme 76 Reduction of the Alkyne to the Alkene in the Presence of Lindlar's Catalyst

¹⁴⁵ The efficiency of the dehydration is not well established. The effect of the drying process on activity and efficiency has been studied: Evans, W.J., Feldman, J.D., Ziller, J.W. *J. Am. Chem. Soc.* **1996**, 118, 4581-4584; Dimitrov, V., Kostova, K., Genov, M. *Tetrahedron Letters* **1996**, 37, 6787-6790.

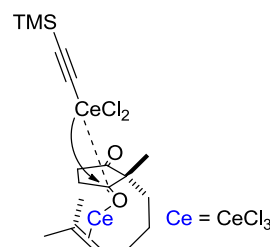
This stereochemistry was confirmed by X-ray crystallographic analysis of the hydrazone derivative **s39** (Scheme 77).



Scheme 77 Preparation of the Hydrazone Derivative of the Propargyl Acetate **s37** and its X-ray Crystal Structure

d) Rationalization

Calculations were performed,¹⁴⁶ according to which CeCl_3 would simultaneously coordinate one carbonyl function and the prenyl moiety so that together with the alkyl chain, it would block one face of the molecule at the same time as activating the carbonyl function, thus accounting for the observed diastereoselectivity (Scheme 78).



Scheme 78 Simultaneous Complexation of CeCl_3 to one Carbonyl Function and the Prenyl Moiety

7. Metal-catalyzed Rearrangement of Propargyl Acetate Precursor **s37**

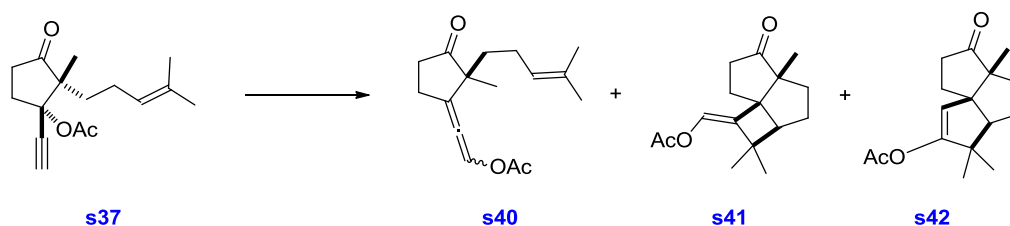
a) Competitive [2+2] and [3+2] Cycloadditions

Propargyl acetate **s37** was engaged into the key metal-catalyzed rearrangement step (Table 16). Different platinum- and gold-based catalysts were tested. With PtCl_2 , a complex mixture was obtained, from which no characterizable product could be isolated (Table 16, entry 1). Fehr reported the possibility of running several platinum- or gold-catalyzed transformations under copper catalysis. Especially, the complementarity of copper catalysis was highlighted.¹⁴⁷ Yet, only the allenyl acetate **s40** could be isolated in 6% yield when $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{BF}_4$ was used as the catalyst (Table 16, entry 2). With all the gold catalysts tested, a mixture of [2+2] and [3+2] cycloaddition products **s41** and **s42** was isolated (Table 16, entries 3-8), the structures of which were determined by X-ray crystallographic analysis of the corresponding hydrazone derivatives

¹⁴⁶ Calculations performed by Dr. Etienne Derat, IPCM.

¹⁴⁷ Fehr, C. *Synlett* **2012**, 23, 990-1006.

(Scheme 80). It is noteworthy that with IPrAuCl and Echavarren's catalyst, the selectivity was reversed in favor of the [3+2] cycloaddition (Table 16, entries 6-8). Also of note, the yield could be remarkably increased by changing the catalyst for {tris(2,4-di-tertbutylphenyl)phosphite}AuCl **s45**, although at the expense of the selectivity since a 1:1 mixture of both cycloaddition products was obtained in this case (Table 16, entry 5).



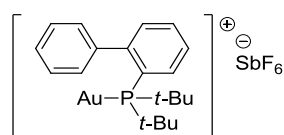
Entry	Catalyst ¹⁴⁸	Reaction conditions	Isolated yield of s40	Isolated yield of s41 and s42	s41:s42 ratio
1	PtCl ₂ (5 mol%)	Toluene, 80°C, 18 h	-	-	-
2 ¹⁴⁹	[Cu(CH ₃ CN) ₄]BF ₄ (5 mol%)	Toluene, 60°C, 4 h	6%	-	-
3	AuCl ₃ (5 mol%)	DCM, r.t., 4 d	-	30%	8.5:1.5
4	Ph ₃ PAuCl + AgSbF ₆	DCM, r.t., 3 h	-	20%	7.5:2.5
5	s45 + AgSbF ₆	DCM, r.t., 2 h	-	76%	5.5:4.5
6 ¹⁵⁰	IPrAuCl + AgSbF ₆	DCM, r.t., 1 h	-	28%	4:6
7	Echavarren's catalyst	DCM, r.t., 1.5 h	44%	-	-
8	Echavarren's catalyst	DCM, r.t., 20 h	-	22%	2.5:7.5

Table 16 Metal-catalyzed Rearrangement of the Propargyl Acetate

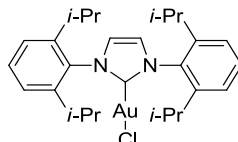
¹⁴⁸ When not mentioned, 2 mol% of the catalyst was used.

¹⁴⁹ The reaction was run under the conditions reported by: Fehr, C., Farris, I., Sommer, H. *Org. Lett.* **2006**, *8*, 1839-1841.

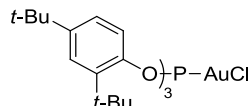
¹⁵⁰ Additional products were isolated. See b) Particular Case of IPrAuCl.



Echavarren's catalyst, **s43**

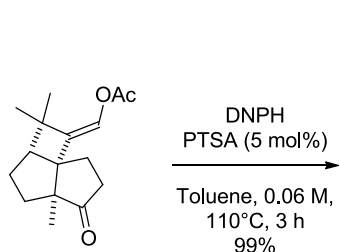


IPrAuCl, **s44**

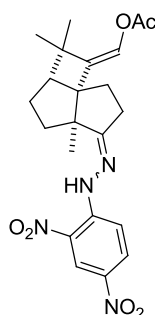


s45

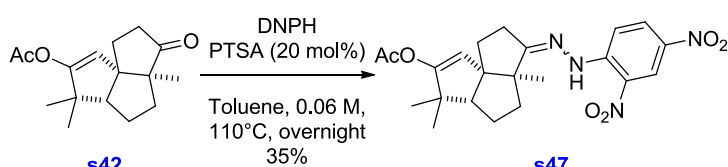
Scheme 79 Gold(I) Catalysts



s41

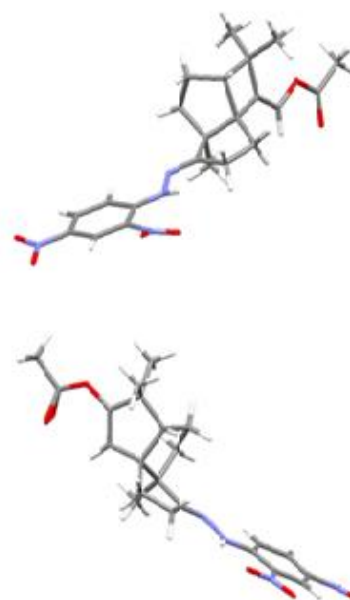


s46



s42

s47



Scheme 80 Formation of the Hydrazone Derivatives of the [2+2] and [3+2] Cycloaddition Products and their Crystal Structures

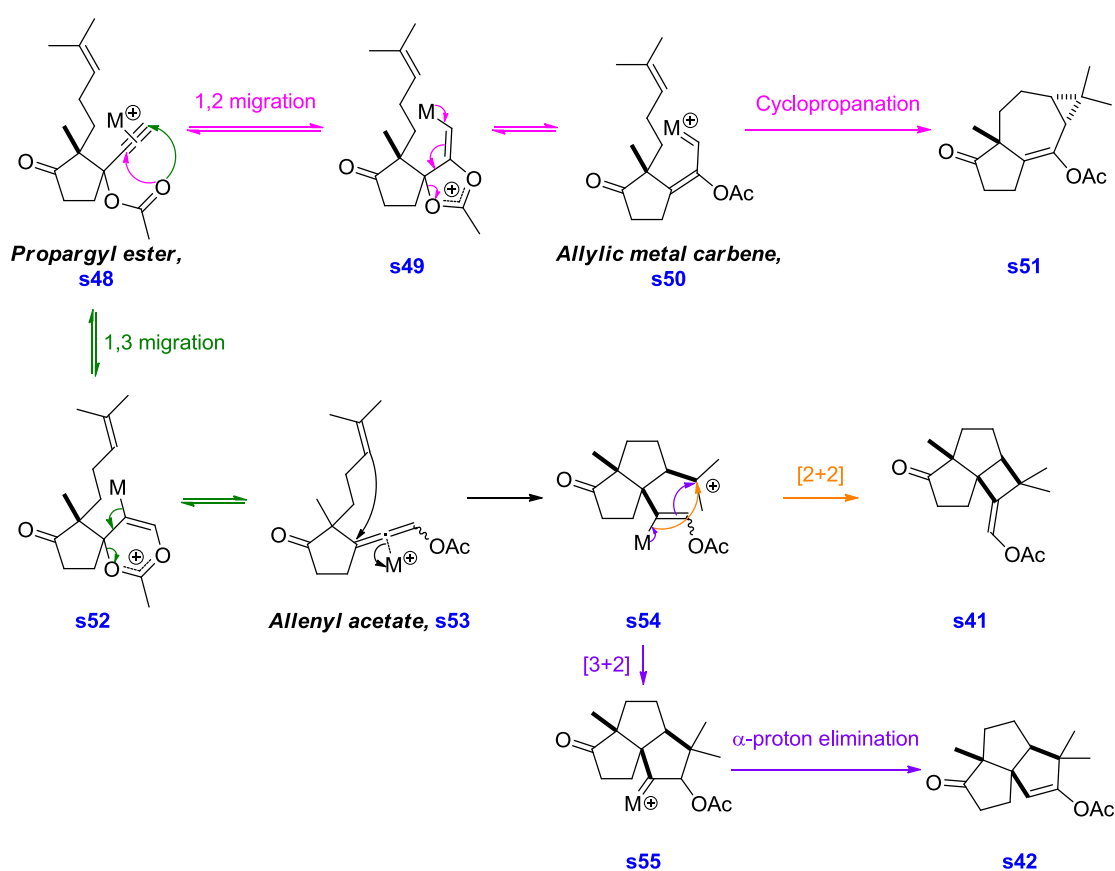
The mechanism of the metal-catalyzed rearrangement of propargyl acetates has been thoroughly studied by Cavallo and co-workers. While PtCl_2 is responsible for a clean 1,2-O-acyl migration (*Scheme 81*, 1,2 migration), under gold catalysis a rapid equilibrium between the propargylic ester (*Scheme 81*, **s48**), allylic metal carbene (*Scheme 81*, **s50**) and allenyl acetate species (*Scheme 81*, **s53**) has been supported by ^{18}O labelling studies.¹⁵¹ Of note, different modes of migration have been found depending on the nature of the catalyst. Thus, a direct 1,2- or 1,3-migration as well as a double 1,2-migration are possible pathways.¹⁵² The mode of migration (1,2- vs. 1,3-O-acyl migration) is dependent on the nature of the electronic group on the alkyne.

¹⁵¹ Marion, N., Lemière, G., Correa, A., Costabile, C., Ramon, R.S., Moreau, X., de Frémont, P., Dahmane, R., Hours, A., Lesage, D., Tabet, J.-C., Goddard, J.-P., Gandon, V., Cavallo, L., Fensterbank, L., Malacria, M., Nolan, S.P. *Chem. Eur. J.* **2009**, *15*, 3243-3260; Correa, A., Marion, N., Fensterbank, L., Malacria, M., Nolan, S.P., Cavallo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 718-721.

¹⁵² Scwier, T., Sromek, A.W., Yap, D.M.L., Chernyak, D., Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868-9878.

In the case of terminal alkynes, 1,2-O-acyl migrations have generally been encountered.¹⁵³ Moreover, the reaction proceeds through competitive pathways, depending on the nature of substrate. Especially, Fürstner claimed initial cycloisomerization followed by [1,2]-O-acyl migration, which was supported by DFT calculations by Soriano.¹⁵⁴

Here, both cycloaddition products **s41** and **s42** arise from the nucleophilic addition of the prenyl moiety onto the allenyl ester activated by gold **s53**. The [2+2] cycloaddition product **s41** is then obtained by direct recombination of the vinyl gold intermediate with the carbocation so formed (*Scheme 81*, **s54**) whereas the formation of the gold carbenoid **s55** followed by α -proton elimination affords the [3+2] cycloaddition product **s42**.¹⁵⁵



*Scheme 81 Proposed Mechanism for the Formation of the [2+2] and [3+2] Cycloaddition Products **s41** and **s42***

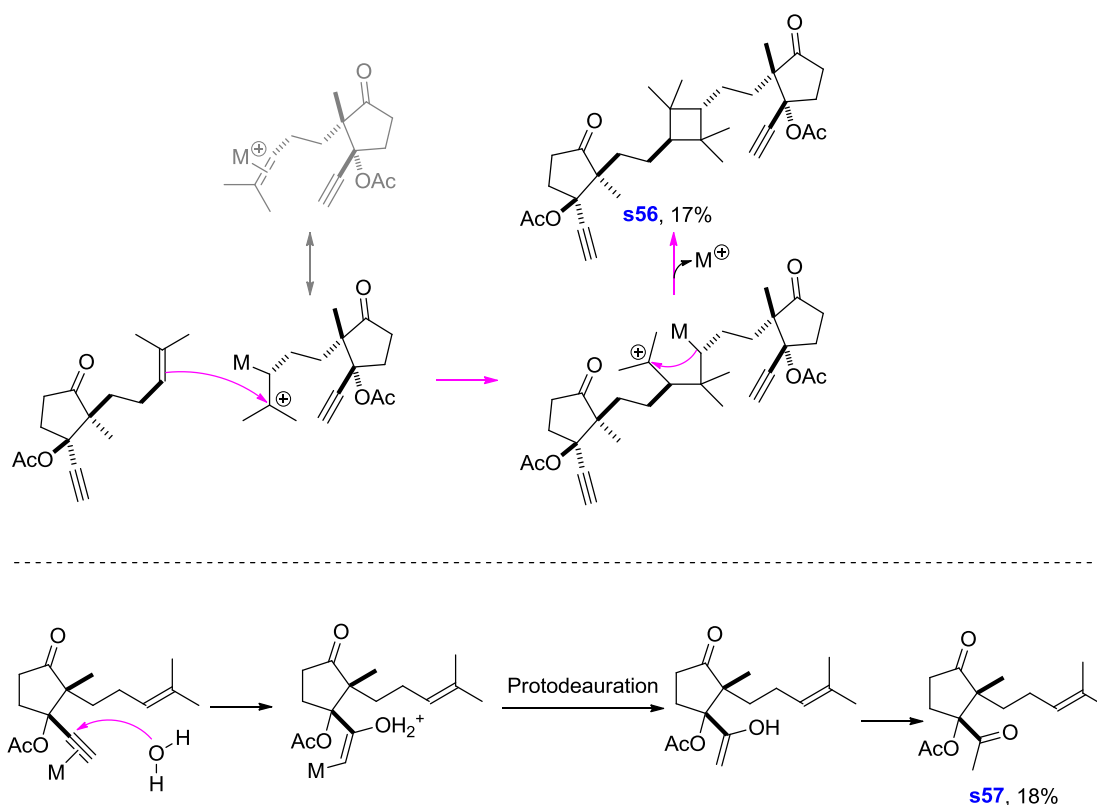
¹⁵³ For examples under $Pt^{(II)}$ catalysis, see: Alison, R.H., Sarpong, R. *Org. Lett.* **2007**, *9*, 4547-4550; Pujanauski, B.G., Bhanu Prasad, B.A., Sarpong, R. *J. Am. Chem. Soc.* **2006**, *128*, 6786-6787; Bhanu Prasad, B.A., Yoshimoto, F.K., Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468-12469; Smith, C.R., Bunnelle, E.M., Rhodes, A.J., Sarpong, R. *Org. Lett.* **2007**, *9*, 1169-1171.

¹⁵⁴ Soriano, E., Marco-Contelles, J. *J. Org. Chem.* **2005**, *15*, 9773-9784; Soriano, E., Ballesteros, P., Marco-Contelles, J. *Organometallics* **2005**, *24*, 3182-3191.

¹⁵⁵ For related work on the [2+2] cycloaddition of Allenenes, see: Luzung, M.R., Mauleon, P., Toste, F.D. *J. Am. Chem. Soc.* **2007**, *129*, 12402-12403. For ligand-controlled access to [4+2] and [4+3] cycloaddition products, see: Mauleon, P., Zeldin, R.M., Gonzalez, A.Z., Toste, F.D. *J. Am. Chem. Soc.* **2009**, *131*, 6348-6349.

b) Particular Case of IPrAuCl

With IPrAuCl, additional products were isolated. The activation of the alkene by gold resulted in the formation of a dimer (*Scheme 82*, **s56**, 17%), and hydration of the alkyne occurred at some point (*Scheme 82*, **s57**, 18%).



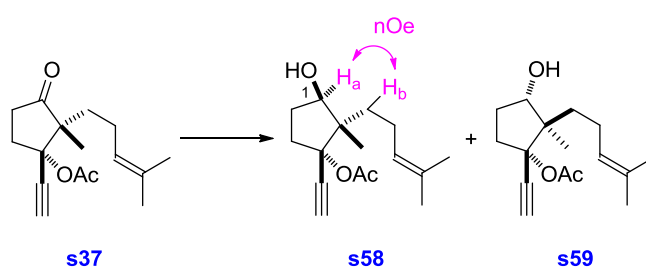
Scheme 82 Proposed Mechanisms for the Dimerization of s37 (Upper Part) and Alkyne Hydration (Bottom Part)

8. Diastereoselective Reduction of the Ketone

a) Reaction on Propargyl Acetate **s37**

Accordingly, the reduction of the ketone into the corresponding alcohol was envisioned, in order to modify the selectivity of the reaction. Firstly, NaBH₄ was employed in a THF/MeOH mixture. This furnished the expected alcohol in good yields but as a 5:1 mixture of inseparable diastereomers (*Table 18*, entry 1). The diastereoselectivity of the reaction was determined by Noesy. Specifically, a nOe correlation between H_a and H_b protons of **s58** was indicative of a *cis*

relationship between the hydroxyl and methyl groups, which may result from the initial coordination of the reducing agent to the acetate function. The influence of the solvent was investigated but no reaction occurred in Et₂O or THF (Table 18, entries 2-3). Nevertheless, when LiBH₄ was used in Et₂O, a single diastereomer was obtained, though the yield was significantly lower (Table 18, entry 4). Interestingly, the reaction was less selective when performed at low temperature (Table 5, entries 5-6). Optimal conditions were finally found to be those where the reaction was run with LiBH₄ in THF as the solvent (Table 18, entry 7). Surprisingly, BH₃.THF lead to complete degradation (Table 18, entry 8).



Entry	Reducing agent	Neq	Solvent	Temperature and time	Isolated Yields	s58:s59 ratio
1	NaBH ₄	4	THF/MeOH 10/1	0°C, 1 h	86%	5:1
2	NaBH ₄	4	Et ₂ O	r.t., 1 h	No reaction	
3	NaBH ₄	4	THF	40°C, 1 h	No reaction	
4	LiBH ₄	1	Et ₂ O	0°C, 1 h	58%	1:0
5 ¹⁵⁶	LiBH ₄	1	THF/MeOH 10/1	0°C, 1 h	-	5:1
6	LiBH ₄	1	Et ₂ O	-5°C, 3.5 h	52%	5:1
7	LiBH ₄	1	THF	0°C, 1 h	80%	1:0
8	BH ₃ .THF	1	THF	66°C	Degradation	

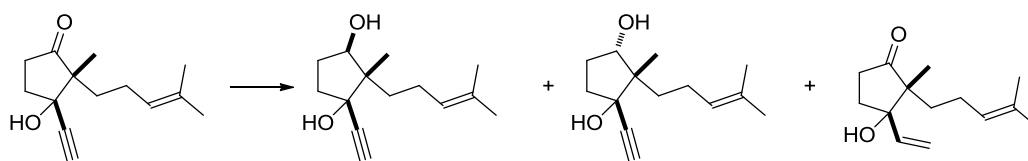
Table 17 Optimization of the Reduction of the Ketone into the Corresponding Alcohol on Propargyl Acetate s37

b) Reaction on Propargyl Alcohol s36

The reduction of the propargyl alcohol precursor s36 was also investigated since the latter should equally be able to coordinate the alkali counteranion and thus direct the reduction toward the formation of s58 (Table 19).

¹⁵⁶ Complete conversion was reached. The crude mixture was not purified.

When LiBH₄ was used at r.t., the reaction resulted in an almost 1:1 ratio of both diastereomers **s60** and **s61** (Table 19, entry 1). At 0°C, a moderate diastereoselectivity was obtained (Table 19, entry 2, 7:3 **s60**:**s61**). At lower temperatures, no reaction occurred or the conversion was very low (Table 19, entry 3). A 1:1 mixture of diastereomers was also obtained in Luche conditions¹⁵⁷ (Table 19, entry 4). No reaction occurred with NaHB(OAc)₃, most probably due to the steric requirement of this reagent (Table 19, entry 5). As for LiAlH₄, the competitive hydroalumination of the triple bond leading to **s62** could not be totally suppressed and unfortunately, this product was inseparable from the diastereomeric diols **s60** and **s61** (Table 19, entries 6-9). Overall, the best result was obtained on propargyl acetate **s37** with LiBH₄ in THF at 0° for 1 h (Table 18, entry 7). Once again, the diastereoselectivity of the reaction was determined by a Noesy experiment indicative of a *cis* relationship between the hydroxyl and methyl groups of **s60**.



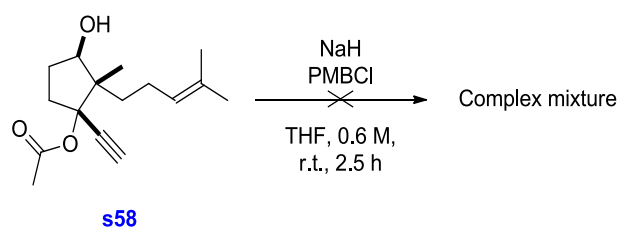
Entry	Reducing agent	Neq	Solvent	Temp	Time	Isolated Yields	Diastereomeric ratios	
							(s60 + s61): s62 ratio	s60 : s61 ratio
1	LiBH ₄	2	Et ₂ O	r.t.	1 h	70%	1:0	1:0.75
2	LiBH ₄	2	Et ₂ O	0°C	1 h	75%	1:0	7:3
3	LiBH ₄	2	Et ₂ O	-50°C	1.3 h		No reaction	
4	NaBH ₄ , CeCl ₃	1.1	MeOH	0°C	30 min	91%	1:0	1:1
5	NaHB(OAc) ₃	8	AcOH	50°C	15 h		No reaction	
6	LiAlH ₄	2	THF	r.t.	30 min	96%	1:1.5	8:2
7	LiAlH ₄	1	THF	0°C	15 min	Quant.	1:0.1	8:2
8	LiAlH ₄	2	THF	-20°C	1.3 h	Quant.	1:0.06	8:2
9	LiAlH ₄ , CeCl ₃	1	THF	-20°C	30 min	Quant.	1:0.06	7:3

¹⁵⁷ Luche, J.L. *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227; Luche, J.L., Rodriguez-Hahn, L., Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601-602; Luche, J.L., Gemal, A.L. *J. Am. Chem. Soc.* **1979**, *101*, 5848-5849.

9. Screening of Catalysts

When the propargyl acetate precursor **s58** featuring a free alcohol in position 1 (see *Table 18*) was reacted in dichloromethane with AuClPPH₃/AgSbF₆ (5 mol%) for 30 minutes at r.t., a complex mixture was obtained, suggesting that the latter should be protected.

Ester protecting groups were not good candidates because of selectivity issues with the enol ester when the cleavage of the latter would be required. The use of the MOM protecting group was envisioned but its removal requires acidic conditions that may trigger the undesired opening of the cyclopropane.¹⁵⁸ Similarly, the removal of the benzyl protecting group by hydrogenolysis or in the presence of a Lewis acid might be detrimental to the integrity of the cyclopropane moiety. Its single electron reductive cleavage or oxidative methods may be preferable.¹⁵⁹ The *p*-methoxybenzyl¹⁶⁰ and 2-methylnaphtalene¹⁶¹ protecting groups are removed more easily than the benzyl protecting group by oxidative cleavage with DDQ. The latter two protecting groups were considered but could unfortunately not be introduced. Two different procedures were tested in order to prepare the PMB-protected alcohol derivative. In the classical conditions where the substrate is stirred for a few minutes with NaH before the addition of PMBCl, total conversion was reached but the reaction led to a complex mixture from which the desired product could not be isolated. Alternatively, sodium hydride was added to the substrate in the presence of PMBCl. Unfortunately, in this case as well, a complex mixture was obtained (*Scheme 83*).



Scheme 83 Attempt for the Preparation of the PMB-Protected Derivative of s58

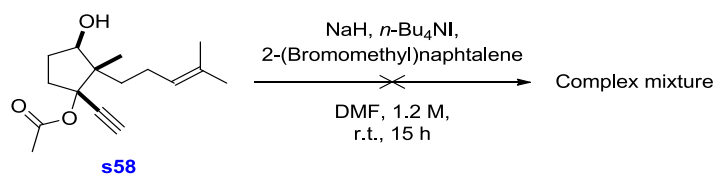
¹⁵⁸ Wuts, P.G.M., Greene, T.W. *Greene's Protective Groups in Organic Synthesis* (A John Wiley and Sons, Inc., Publication), Fourth edition, **2007**, p.30.

¹⁵⁹ Wuts, P.G.M., Greene, T.W. *Greene's Protective Groups in Organic Synthesis* (A John Wiley and Sons, Inc., Publication), Fourth edition, **2007**, p.102.

¹⁶⁰ Wuts, P.G.M., Greene, T.W. *Greene's Protective Groups in Organic Synthesis* (A John Wiley and Sons, Inc., Publication), Fourth edition, **2007**, p.121.

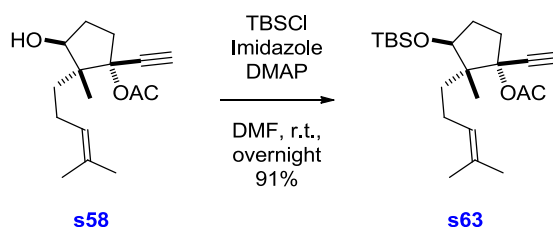
¹⁶¹ Gaunt, M.J., Yu, J., Spencer, J.B. *J. Org. Chem.* **1998**, *63*, 4172-4173.

When it comes to the 2-methylnaphthyl ether protecting group, two different procedures were also tested. In the reported procedure, 2-(Bromomethyl)naphthalene is used along with *n*-Bu₄NI and Dipea. In those conditions, however, no reaction occurred and both the starting material and 2-(Bromomethyl)naphthalene were recovered. When the substrate was deprotonated previously to the addition of *n*-Bu₄NI and 2-(Bromomethyl)naphthalene, total conversion was reached. Unfortunately, a complex mixture was obtained after removal of the excess 2-(Bromomethyl)naphthalene by flash column chromatography on silica gel (*Scheme 84*).



Scheme 84 Attempt for the Preparation of the 2-methylnaphthyl Ether Derivative

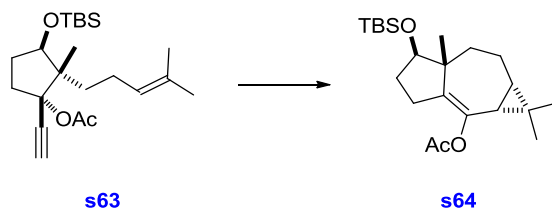
We turned our attention to silyl derivatives because in contrast, the removal of silyl protecting groups in the presence of fluoride appears as smooth conditions that are more likely not to be detrimental to the integrity of the molecule. The robust TBDMS group was thus selected. To our delight, s58 was successfully protected into its TBS derivative (*Scheme 85*).



Scheme 85 Protection of s58 into its TBS Derivative

The resulting TBS-protected propargyl acetate **s63** was then engaged into the metal-catalysed rearrangement step. Once again, platinum, copper and gold catalysts were explored. PtCl₂ and [Cu(CH₃CN)₄]BF₄ were not effective in this case either (*Table 20, entries 1 and 7, respectively*). A poor influence of the ligand on gold was noticed in this case, all catalysts leading to the expected product as the very major one, in similar yields (35-45%) (*Table 20, entries 2-6*). A slightly lower yield was obtained with tris(2,4-di-*tert*butylphenyl)phosphiteAuCl **s45** as the catalyst (*Table 20, entry 6*). The reaction was much faster with cationic gold(I) catalysts than with AuCl₃ (*Table 20, entries 3-6 and 2,*

respectively). A prolonged reaction time was not beneficial to the reaction. Scaling-up the reaction did not alter the yield (*Table 20, entry 5*).



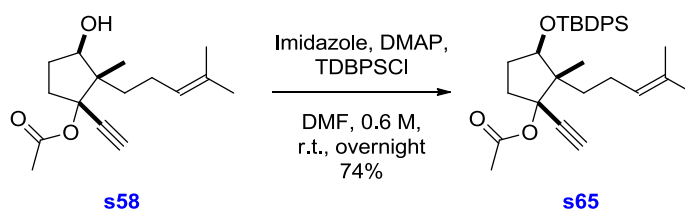
Entry	Scale	Catalyst	Reaction time	Solvent and temperature	Isolated Yields
1	0.2	PtCl ₂	5.6 h	Toluene, 80°C	0
2	0.2	AuCl ₃	7.2 h	DCM, r.t.	46%
3	0.2	Ph ₃ PAuCl + AgSbF ₆	5 min	DCM, r.t.	41%
4	0.2	Echavarren's catalyst	5 min	DCM, r.t.	48%
5	1 mmol	Echavarren's catalyst	3 h	DCM, 0°C	46%
6	0.2	s45 + AgSbF ₆	5 min	DCM, r.t.	33%
7	0.2	[Cu(CH ₃ CN) ₄]BF ₄	5 min	Toluene, 110°C	Degradation

Table 19 Metal-catalyzed Rearrangement of the Propargyl Acetate s63

10. Screening of Protecting Groups

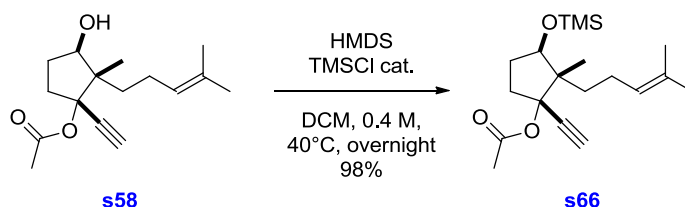
Aiming at the further optimization of the reaction, various other protecting groups than TBS were investigated, with different steric and/or electronic properties. Their preparation is discussed below.

The TBDPS group was introduced in the same reaction conditions than TBS. Worthy of note, the transformation required large quantities of the reagents and a prolonged reaction time for the conversion for the conversion to be total, showing how hindered the secondary alcohol is, in α position to a neopentyl centre. The desired compound could nonetheless be isolated in 74% yield (*Scheme 86*).



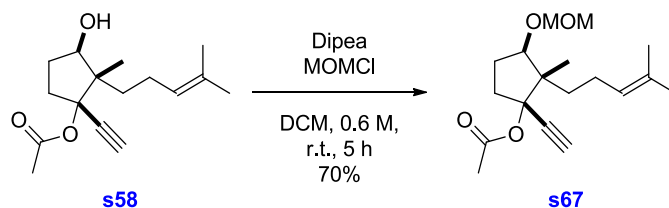
Scheme 86 Preparation of the TBDPS-Protected Derivative of s58

A different method was used in order to prepare the TMS-protected derivative **s66** (*Scheme 87*). The expected compound was obtained in excellent yields on condition that the reaction was performed at 40°C and stirred at this temperature overnight, and could be engaged in the next step without any purification. No reaction occurred when the reaction was run at room temperature, which once again is indicative of the substantial steric hindrance that need to be overcome.



Scheme 87 Preparation of the TMS-Protected Derivative of s58

Non silylated protecting groups were also explored. The MOM-protected alcohol was formed in very classical conditions using DIPEA and MOMCl in DCM (*Table 21*). As in the case of the TBDPS group, the reaction required large quantities of the reagents but proceeded smoothly to afford the desired product **s67** in 70% yield (*Table 21, entry 2*).



Entry	Neq Dipea	Neq MOMCl	Conversion	Isolated Yields
1	2.2	2	70%	57%
2	6.6	6	Total	70%

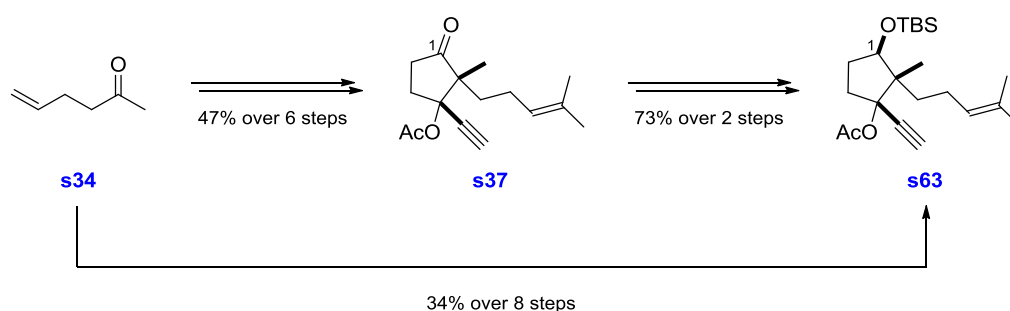
Table 20 Preparation of the MOM-protected Alcohol Derivative

These various derivatives of the propargyl acetate were submitted to the rearrangement under the same conditions as those previously optimized with the TBS-protected alcohol. The

outcome of the reaction was unchanged, so that the TBS protecting group was kept at the protecting group of choice. The intermediate **s64** so obtained in the gold-catalyzed rearrangement of propargyl acetate **s63** is common to both the total syntheses of (\pm)-Neomeranol and (\pm)-Valeneomerin B.

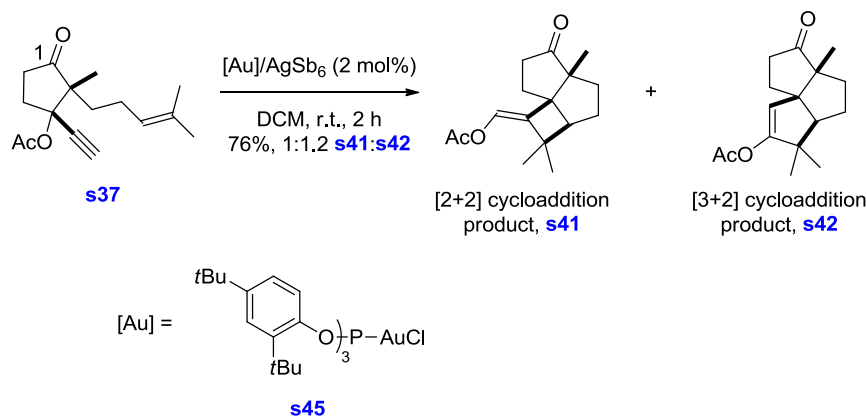
11. Conclusion and Perspectives

To conclude, we have developed efficient and reproducible diastereoselective syntheses of propargyl acetate precursors (*Scheme 88*), which were successfully engaged into the gold-catalyzed rearrangement of the propargyl acetate to furnish cycloaddition and cyclopropanation products depending on the substrate pattern.



Scheme 88 Syntheses of Propargyl Acetate Precursors s37 and s63

When in position 1 there is a ketone (*Scheme 89*, **s37**), cycloaddition products **s41** and **s42** arising from the nucleophilic addition of the prenyl moiety to the gold-coordinated allenyl ester are obtained (*Scheme 89*). Interestingly, the ratio between the two cycloaddition products is highly dependent on the nature of the catalyst used, with the sterics rather than electronic properties of the latter being determining.



Scheme 89 Formation of [2+2] and [3+2] Cycloaddition Products in the Gold-Catalyzed Rearrangement of Propargyl Acetate

The efficiency of the reaction, however, seems to be dependent on the electronic properties of the gold-catalyst. Especially, the yield was greatly improved with the poor electron-donating triphosphite ligand **s45**. Thus, one can imagine the rate determining step of this reaction to be the Lewis-acid activation of the allenyl ester intermediate.

When in position 1 there is a TBS-protected alcohol, the desired cyclopropanation product was obtained as the very major product one. In this case, however, a poor influence of the gold-catalyst on the outcome of the reaction was observed.

One may propose a W conformation between the oxygen atom of the ketone function (or TBS-protected alcohol) and C5, responsible for a long distance inductive effect (as compared to long distance coupling constants attributed to such W conformations). When in position 1 there is a ketone, the mesomeric attractive effect from the oxygen atom renders the partial positive charge developed in position 1 and thus the strength of the inductive effect stronger. Therefore, the allenyl ester intermediate would be more electrophilic in this case, and the activation energy required for the cycloaddition pathway lowered (*Figure 3*).

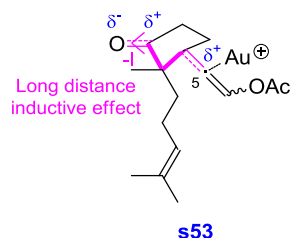
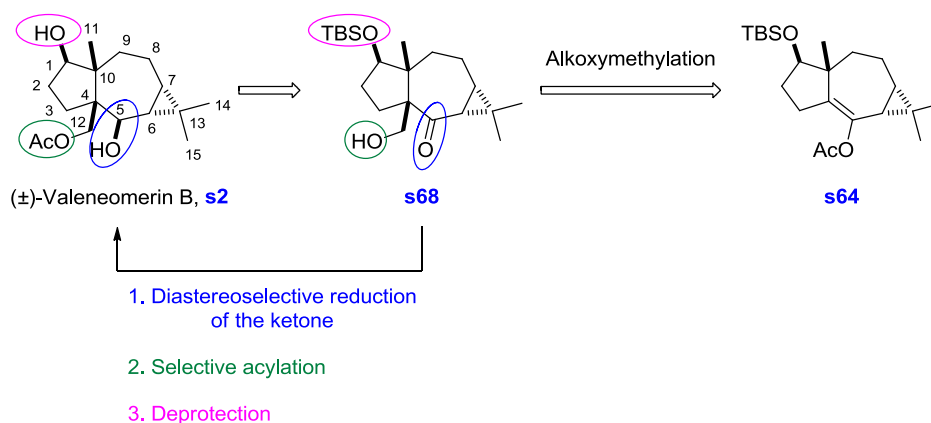


Figure 3 Proposed Long distance Inductive Effect in the Allenyl Ester Intermediate

III. Studies Toward the Total Synthesis of Valeneomerin B - Total synthesis of (±)-5-epi-Valeneomerin B

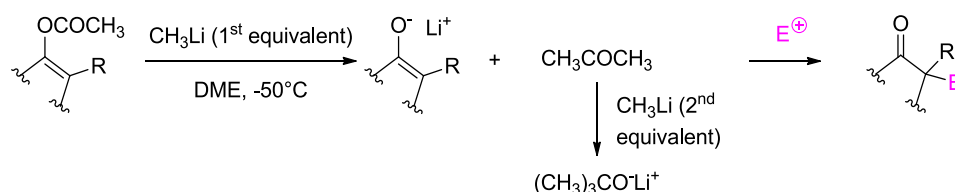
1. Alkoxy methylation of the Vinyl Acetate

With cyclized intermediate **s64** in hands, we turned our attention toward the total synthesis of (\pm)-Valeneomerin B. For this purpose, we planned the diastereoselective alkoxy methylation of the enol acetate function of **s64**, followed by the diastereoselective reduction of the resulting ketone in **s68**, selective acylation of the primary alcohol (in position 12) and finally removal of the TBS-protecting group (*Scheme 90*). We envisioned the diastereoselective reduction of the ketone in position 5 of **s68** to be difficult (requiring harsh conditions). For this reason and in order to avoid competitive reduction between ketone and acetate functions, we chose to perform the reduction of the ketone (in position 5) preliminary to the acylation of the primary alcohol (in position 12). Besides, the deprotection was planned as the last step of the synthesis in order to facilitate the selective acylation of the primary alcohol in position 12 (to avoid selectivity issues between the primary alcohol in position 12 and the secondary alcohol in position 1).



*Scheme 90 Retrosynthetic Analysis (Upper Part) and Synthetic Planning (Bottom Part) of (\pm)-Valeneomerin B **s2***

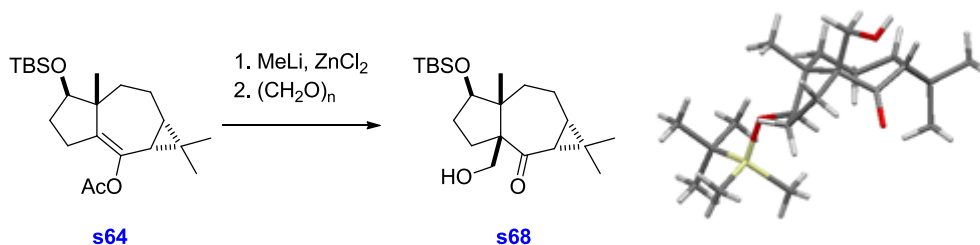
Vinyl acetates have been exploited as precursors for the regioselective formation of lithium enolates upon treatment with 2 equivalents of MeLi. Then, the enolate can be trapped in the presence of an electrophile (*Scheme 91*).¹⁶²



Scheme 91 Consumption of 2 equiv. of MeLi in the Conversion of Enol Acetates into the Corresponding Lithium Enolates

¹⁶² House, H.O., Trost, B.M. *J. Org. Chem.* **1965**, *30*, 2502-2512; Anastasis, P., Brown, P.E., Islam, Q., Marcus, W.Y. *Journal of Chemical Research, Synopsis* **1989**, *2*, 36-37.

After treatment of enol acetate **s64** with 2 equivalents of MeLi, anhydrous ZnCl₂ was added to the reaction mixture. Li→Zn transmetalation occurred so that a zinc enolate was formed. Since zinc enolates are mostly centered on the carbon atom,¹⁶³ this allows the enolate intermediate to react preferentially *via* C-alkylation and thus to avoid O-alkylation. For an alkoxymethyl group to be introduced, formaldehyde should be used as the electrophile. Since the latter is a gas and thus is difficult to handle, dry paraformaldehyde (which is a solid) was used instead. Yet it was introduced in excess (5 equiv.) due to its lower reactivity (the addition of more than 5 equivalents of paraformaldehyde did not improve the yield of the reaction). The expected product could be isolated in a moderate yield, and the reaction scaled-up without any significant alteration of it (Table 22, entries 1-2). No reaction occurred, however, when MeLi was replaced with MeONa (Table 22, entry 3). Of note, cyclized product **s64** can be engaged directly into the alkoxymethylation step without purification. Importantly, the reaction was totally diastereoselective. The stereochemistry of compound **s68** has been confirmed by X-ray crystallographic analysis. It is likely that the carbanion formed is in a *cis* relationship with the angular methyl so that a less strained 5-membered-ring is obtained. Unlike radicals, carbanions do not tend to invert. Then, the fact that the molecule is bent probably prevents the electrophile to approach from the inner side of the molecule.



Entry	Nucleophile	Scale	Temperature	Reaction time	Isolated Yields
1	MeLi	0.1 mmol	0°C	1 h	50%
2	MeLi	1 mmol	0°C → r.t.	Overnight	47%
3	MeONa	0.1 mmol	0°C	1 h	No reaction

Table 21 Stereoselective Alkoxymethylation of Vinyl Acetate **s64**

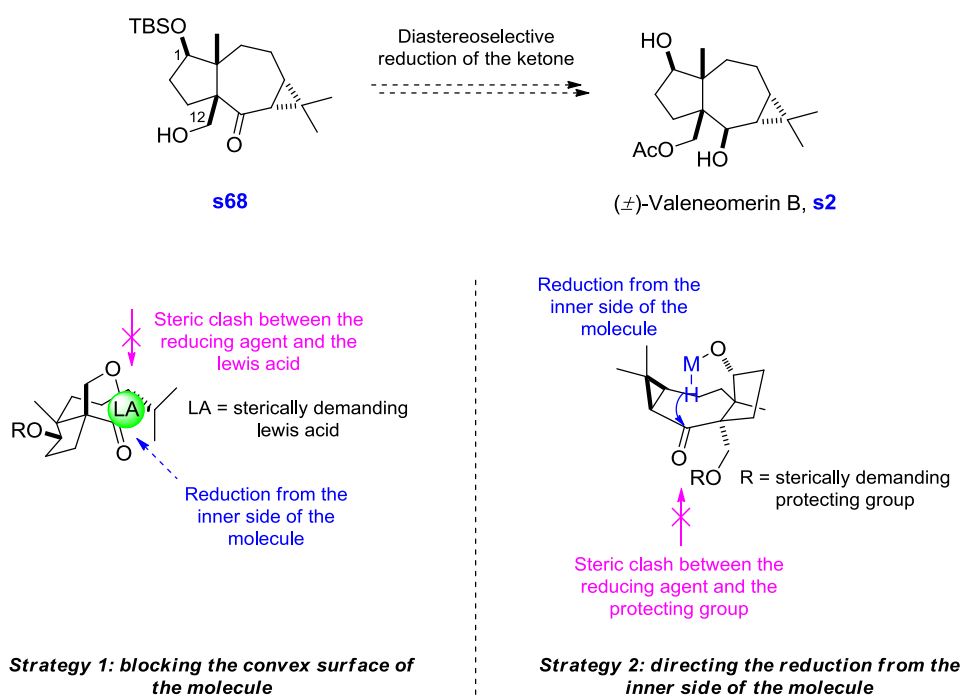
2. Reduction of the Ketone

¹⁶³ For reviews on zinc enolates, see: Baba, A., Yasuda, M., Nishimoto, Y. *Comprehensive Organic Synthesis* (2nd Edition) **2014**, 2, 523-542; Heathcock, C.H. *Comprehensive Organic Synthesis* (2nd Edition, Edited by Knochel, P., Molander, G.A.) **2014**, 2, 340-395; Perez-Luna, A., Botuha, C., Ferreira, F., Chemla, F. *New J. Chem.* **2008**, 32, 594-606; Banon-Tenne, D., Marek, I. *Transition Metals for Organic Synthesis* (2nd Edition, Edited by Beller, M., Bolm, C.) **2004**, 1, 563-573.

The diastereoselective reduction of the ketone was required. For the right diastereomer to be formed, the reduction should occur from the more hindered side of the molecule, which is unlikely. For this purpose, two strategies were envisioned:

-On the one hand, the primary alcohol (in position 12) may be used to block the convex surface of the molecule *via* its coordination to a sterically demanding Lewis acid (*Scheme 92, Strategy 1*).

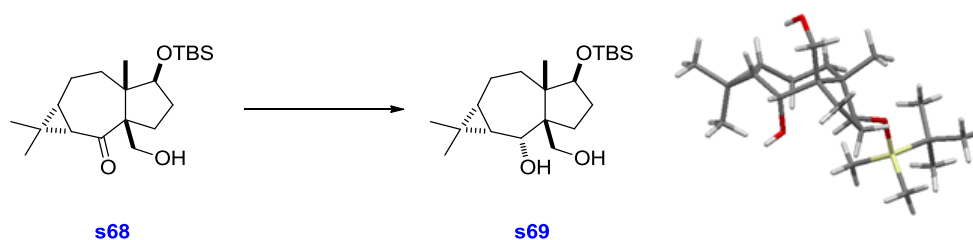
-Alternatively, the secondary alcohol (in position 1) may be used to direct the reduction from the inner side of the molecule (*Scheme 92, Strategy 2*).



Scheme 92 Strategies Envisioned for the Diastereoselective Reduction of the Ketone in Alkoxyethylated Compound s68

a) Strategy 1: Blocking the Convex Surface of the Molecule

The large CeCl_3 salt was used in MeOH along with NaBH_4 in order to both activate the ketone and block the convex surface of the molecule. Unfortunately, no reaction occurred in these conditions, probably because the reducing agent formed from NaBH_4 and MeOH is too sterically demanding for an approach from the inner side of the molecule to be allowed (*Table 23, entry 1*). The smaller LiBH_4 did not give better results in THF as the solvent), with the wrong diastereomer being isolated in only 30% yield. (*Table 23, entry 2*). The use of DIBAL-H was also envisioned, the first equivalent being intended to block the convex surface of the molecule. Although the yield was slightly improved in this case, the expected diastereomer could not be formed (*Table 23, entry 3*).

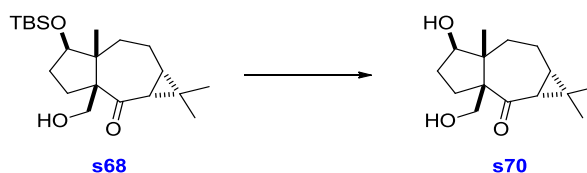


Entry	Reducing agent	Nequiv.	Solvent	Temperature and reaction time	Isolated Yields
1	NaBH ₄ , CeCl ₃	1	MeOH	0°C	No reaction
2	LiBH ₄ , CeCl ₃	1	THF	50°C	30%
3	DIBAL-H	2	DCM	40°C, overnight	49%

Table 22 Reduction of Ketone **s68** in the Presence of a Sterically Demanding Lewis Acid

b) Strategy 2: Directing the Reduction from the Inner Side of the Molecule

On the basis of the crystallographic structure of ketone **s68**, we did consider the possibility of the reduction from the inner side of the molecule, with the secondary alcohol as a directing group. For this purpose, the TBS protecting group required to be removed. In the presence of TBAF, unfortunately, the expected product was obtained in only 34% yield (Table 24, entry 1). With HF.pyridine, no reaction occurred at all (Table 24, entry 2).

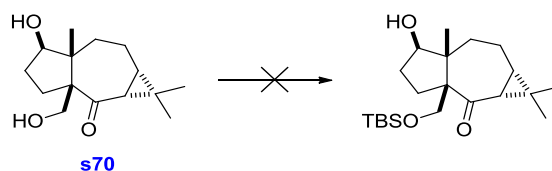


Entry	Reagent	Reaction conditions	Isolated Yields
1	TBAF	THF, 0.09 M	34%
2	HF.pyridine	THF, r.t., overnight	No reaction

Table 23 Removal of the TBS Protecting Group

i. Studies toward the Selective Protection of the Primary Alcohol

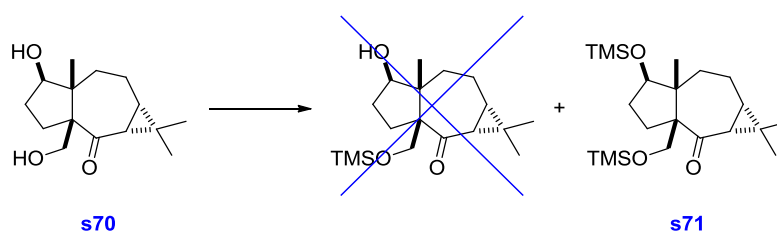
The selective protection of the primary alcohol (vs. the secondary alcohol) proved to be difficult. Surprisingly, the TBS-protecting group could not be introduced, even upon heating at 120°C overnight (*Table 25, entry 1*). On the other hand, preliminary deprotonation of the hydroxyl groups did not allow the reaction to proceed either (*Table 25, entry 2*).



Entry	Reagents	Conditions	Outcome
1	TBSCl, imidazole, DMAP	DMF, 120°C, overnight	No reaction
2	TBSCl, NaH	THF, r.t., overnight	No reaction

Table 24 Attempts toward the Selective Protection of the Primary Alcohol with TBSCl

With the smaller TMS-protecting group, selectivity between the primary and secondary alcohols could not be achieved. In the presence of 1 equiv. of TMSCl and imidazole, no reaction occurred, even at 80°C (*Table 26, entry 1*). No reaction occurred either when HMDS was used at r.t. along with TMSCl (*Table 26, entry 2*). In contrast, the bis silylated compound was obtained upon increasing the equivalent HMDS and reaction temperature (*Table 26, entry 3*).

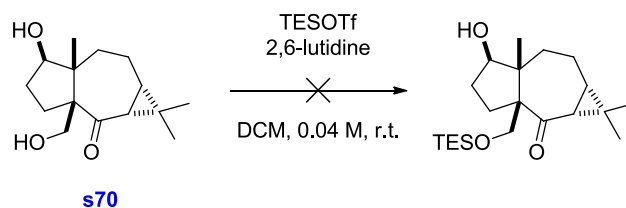


Entry	Reagents	Conditions	Outcome
1	HMDS (1 equ.), TMSCl cat.	DCM, 0.04 M, 40°C	77% of the bis silylated compound
2	HMDS (0.5 equ.), TMSCl cat.	DCM, 0.04 M, r.t., overnight	No reaction
3	TMSCl, imidazole	DMF, 80°C, 1 h	No reaction

Table 25 Attempts Toward the Selective Protection of the Primary Alcohol with TMSCl

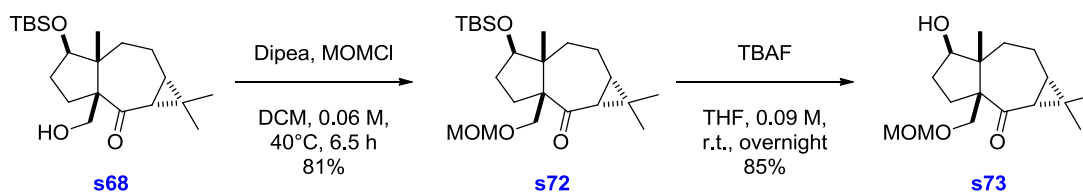
In order to get a selective reaction, the TES protecting group was considered. TESOTf was indeed thought to be reactive enough for the reaction to occur. On the other hand, the TES

group is larger than the TMS, so that the reaction might be selective. Unfortunately, no reaction occurred (*Scheme 93*).



Scheme 93 Attempt Toward the Selective Protection of the Primary Alcohol with TESOTf

Consequently, the primary alcohol was protected prior to the cleavage of TBS. A protecting group orthogonal to it was therefore required. The MOM group was chosen, because MOM ethers can be converted directly to an acetate in the presence of Ac_2O and a Lewis acid such as FeCl_3 or InI_3 ,¹⁶⁴ thus avoiding a deprotection step and allowing the selective introduction of the acetate function of (\pm)-Valeneomerin B. Then, the TBS group was removed with TBAF (*Scheme 94*).

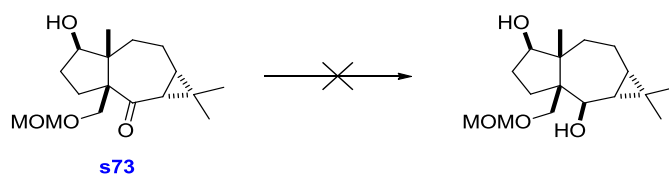


Scheme 94 Protection of the Primary Alcohol and Selective Deprotection of the Secondary Alcohol

ii. Screening of Reducing Agents

With this precursor in hands, various reducing agents were tested. No reaction occurred neither with 1 or 2 equivalents of LiBH_4 (*Table 27, entries 1-2*), nor with LiAlH_4 or DIBAL-H (*Table 24, entries 3 and 4, respectively*).

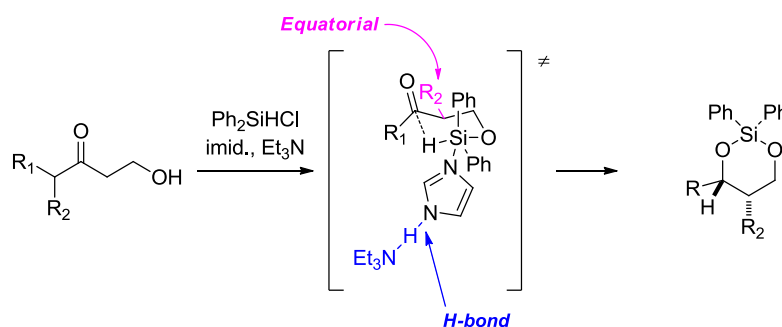
¹⁶⁴ Wuts, P.G.M., Greene, T.W. *Greene's Protective Groups in Organic Synthesis* (A John Wiley and Sons, Inc., Publication), Fourth edition, **2007**, p.30; Bosch, M.P., Petschen, I., Guerrero, A. *Synthesis* **2000**, 300; Ranu, B.C., Hajra, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 355.



Entry	Reducing agent	Reaction conditions	Outcome
1	LiBH ₄ (1 equiv.)	THF, 0.05 M, 66°C, 1 h	No reaction
2	LiBH ₄ (2 equiv.)	THF, 0.02 M, 66°C, 1 h	No reaction
3	LiAlH ₄	THF, 0.03 M, 66°C	No reaction
4	DIBAL-H (2.2 equiv.)	DCM, 0.04 M, 40°C, overnight	No reaction
5	Et ₃ N, imidazole, diphenylchlorosilane	DCM, 0.1 M, r.t., overnight	No reaction

Table 26 Attempts toward the Reduction of Ketone **s73** from the Inner Side of the Molecule

Inspired from the work of O’Neil and co-workers,¹⁶⁵ diphenylchlorosilane was used along with imidazole and Et₃N. Under these conditions, β-hydroxy ketones are converted directly to cyclic siloxane products. The mechanism of the reaction was proposed to involve nucleophilic activation at silicon by imidazole to generate a transient hydrosilanide. The developing negative charge on silicon can be stabilized by each phenyl substituent and the positively charged imidazolium by hydrogen bonding/abstraction with trimethylamine. Hydride is delivered from silicon *via* a six-membered chairlike transition state (Scheme 95). Unfortunately, no reaction occurred under these conditions either (Table 27, entry 5).

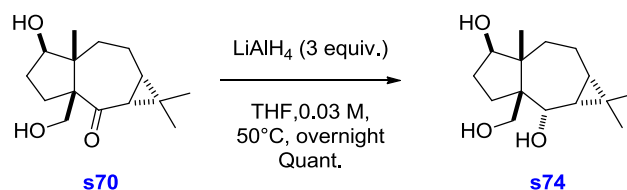


Scheme 95 Proposed Mechanism for the Intramolecular Hydrosilylation reaction in the Presence of Ph₂SiHCl

c) With both Primary and Secondary Alcohols Free

¹⁶⁵ Medina, C., Carter, K.P., Miller, M., Clark, T.B., O’Neil, G.W. *J. Org. Chem.* **2013**, 78, 9093-9101.

With the dihydroxylated compound as starting material, the reaction yielded the wrong diastereomer (*Scheme 96*).



Scheme 96 Reduction of Ketone s70 in the Presence of LiAlH₄

3. Inversion of the Alcohol

a) Mitsunobu Reaction

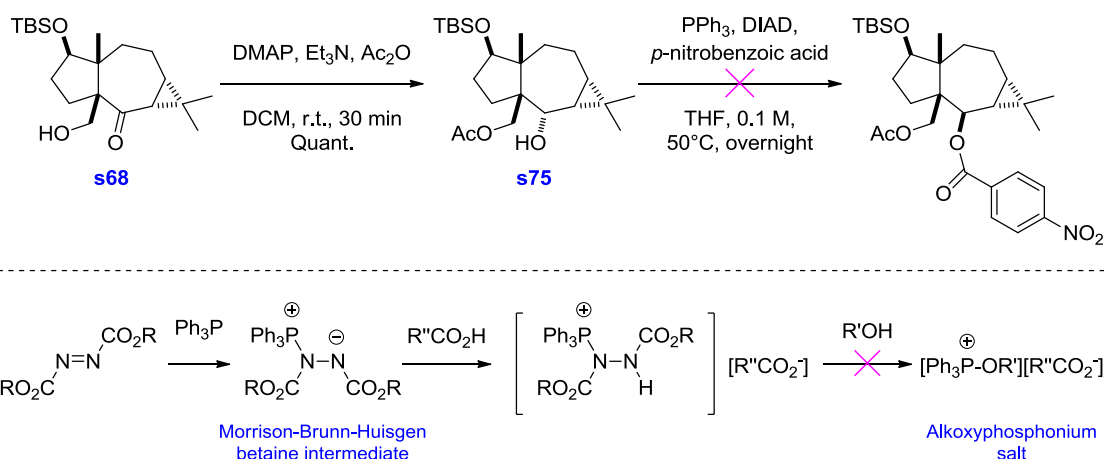
Because the formation of the desired diastereomer was not observed, the inversion of the configuration of the alcohol (in position 5) was considered. In order to prevent the free primary alcohol (in position 12) from interfering in the Mitsunobu reaction, the latter was selectively acylated upon the use of one equivalent of Ac₂O (*Scheme 97*, upper part). This acetate function is retained in (±)-Valeneomerin B.

The Mitsunobu reaction depends upon an S_N2-type backside displacement and thus is subject to the steric requirements inherent in the S_N2 process. Martin and Dodge recommended the use of *p*-nitrobenzoic acid in the inversion of relatively hindered secondary alcohols. The neopentyl system, however, is one of the poorest candidates for an S_N2 inversion process. Not only is the steric impediment virtually insurmountable but the competing S_N1 component occurs with a pinacolic type rearrangement.¹⁶⁶

The Mitsunobu process involves initial irreversible formation of the Morrison-Brunn-Huisgen intermediate¹⁶⁷ which is a substantially bulky reagent. The inversion failed, likely because of a steric effect in the initial activation process $\text{Ph}_3\text{P}^+\text{N}(\text{CO}_2\text{R})\text{NHCO}_2\text{R} + \text{R}'\text{OH} \rightarrow \text{Ph}_3\text{P}^+(\text{OR}') + [\text{NH}(\text{CO}_2\text{R})]_2$ (*Scheme 97*, bottom part).

¹⁶⁶ Zelinski, N., Zelikow, J. *Ber.* **1901**, 34, 3249.

¹⁶⁷ Crich, D., Dyker, H., Harris, R.J. *J. Org. Chem.* **1989**, 54, 257.



Scheme 97 Acetylation of the Primary Alcohol (Upper Part) and Attempt for Mitsunobu Inversion (Bottom Part)

b) Moriarty's Conditions for the Inversion of Highly Hindered Alcohols

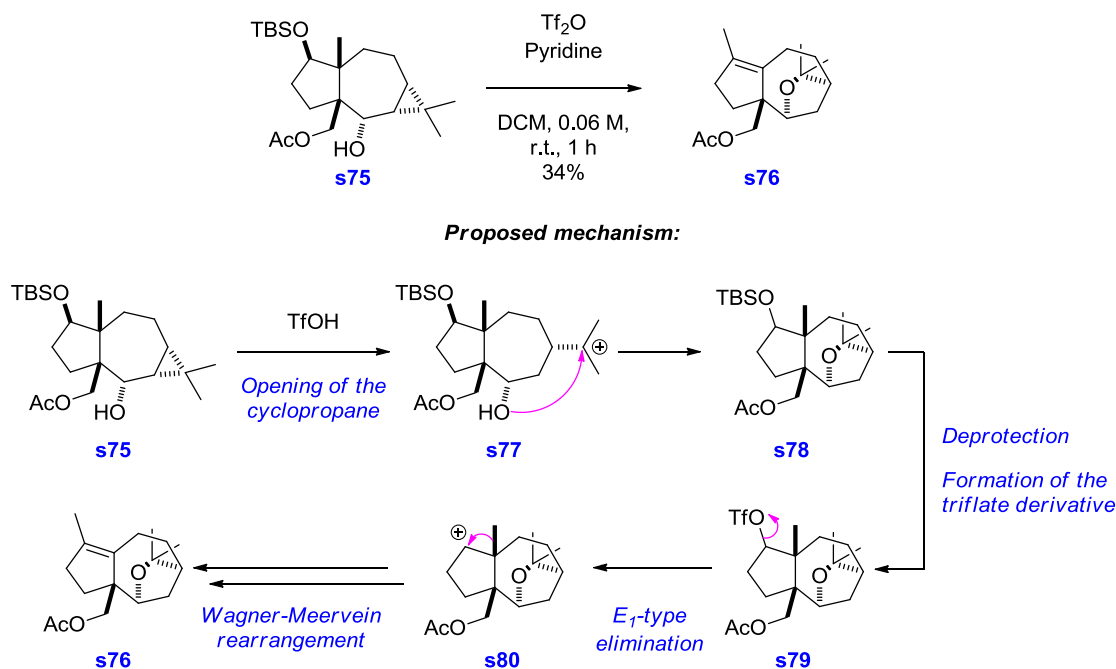
Moriarty reported conditions for the inversion of configuration of α -trisubstituted (neopentyl) type secondary alcohols based on the use of an esterifying agent for the alcohol of low steric demand, and one which converts the alcohol into a strongly nucleofugic group. On the other hand, an anionic partner of low steric demand which is strongly nucleophilic in a dipolar protic solvent is needed. The triflate ester as well as the nitrite anion fit both the steric and electronic requirements.¹⁶⁸ Operationally, potassium nitrite was added to the triflate dissolved in DMF, along with a catalytic amount of 18-crown-6. A range of α -tertiary systems underwent the inversion in excellent chemical and stereochemical yields. Mesylate esters have also proved competent in this reaction and, subsequently, carboxylates have mostly been used as nucleophiles. Of note, this inversion process is the only one which works for α -tertiary systems. From a mechanistic standpoint, ¹H NMR indicated the formation of a nitrite ester which hydrolyses *in situ*.

When alcohol **s75** was reacted in the presence of Tf₂O and pyridine, however, complex rearrangements occurred, indicative of the presence of triflic acid in the reaction medium (Scheme 98). In the presence of a strong acid, indeed, the cyclopropane opens because the resulting carbocation is stabilized by the two methyl groups (Scheme 98, **s77**).¹⁶⁹ The carbocation was then trapped by the free alcohol (in position 5) to afford **s78**. Independently, the TBS-protecting group is cleaved in strong acidic conditions so that a triflate ester was likely formed,

¹⁶⁸ Stang, P.J., Hanack, M., Subramanian, L.R. *Synthesis* **1982**, 85; Kornblum, N. *Org. Reactions* **1962**, 12, 101.

¹⁶⁹ Ishmuratov, G.Y., Vydrina, V.A., Yakovleva, M.P., Galkina, Y.A., Lobko, I.F., Muslukhov, R.R., Vyrypaev, E.M., Tolstikov, A.G. *Russian Journal of Organic Chemistry* **2012**, 48, 1210-1215.

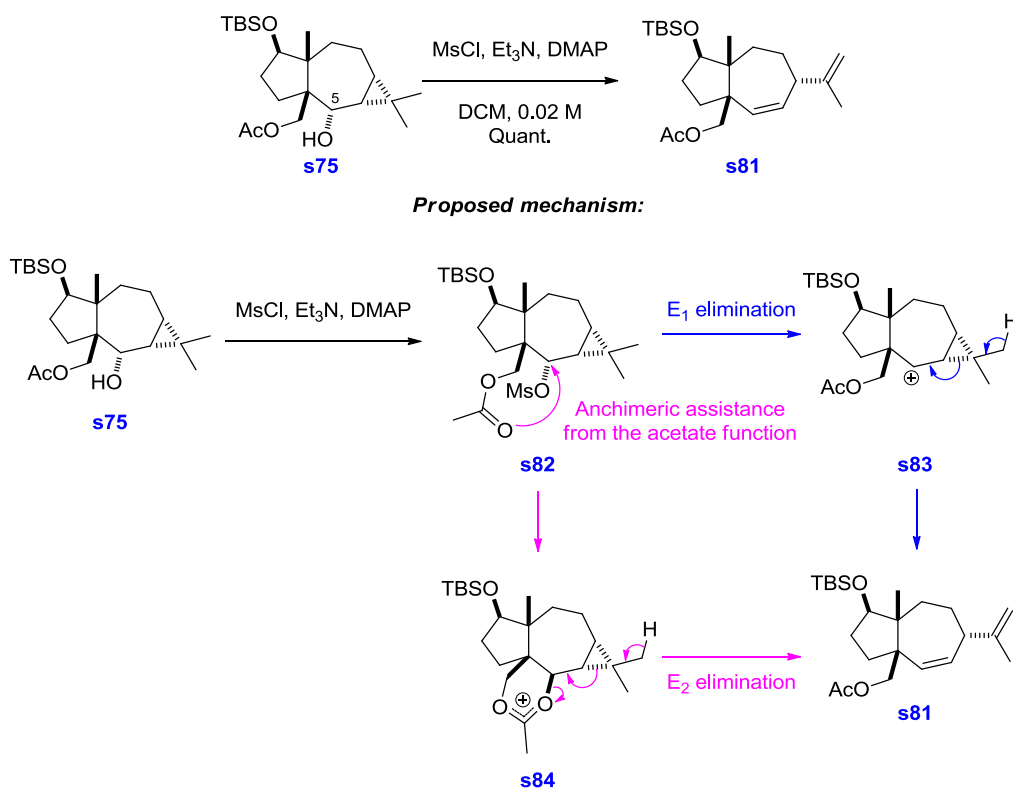
that led to a carbocation *via* a E_1 -type elimination (*Scheme 98*, **s80**). Finally, a Wagner-Meerwein rearrangement occurred, followed by proton elimination, leading to **s76**.



Upon the use of MsCl, quantitative yields of the diene resulting from the opening of the cyclopropane were obtained. From a mechanistic point of view, either a carbocation was formed in position 5 (*Scheme 99*, E_1 elimination pathway),¹⁷⁰ or anchimeric assistance from the acetate group is to be considered (*Scheme 99*, E_2 elimination pathway).¹⁷¹ It is likely that both mechanisms are at stake.

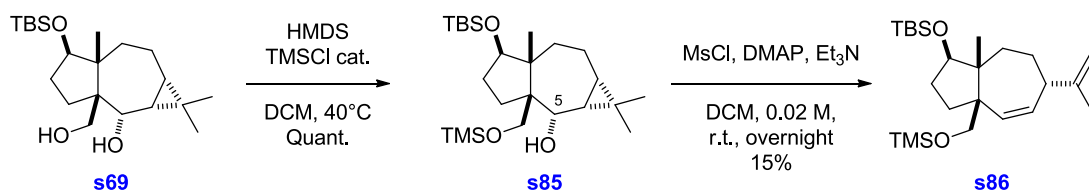
¹⁷⁰ For an example of E_1 elimination, see: Srikrishna, A., Vijaykumar, D. *Tetrahedron Lett.* **1998**, 39, 5833-5834.

¹⁷¹ For examples of anchimeric assistance from acetates, see: Al-Hussini, A.H., Moore, H.W. *J. Org. Chem.* **1985**, 50, 2597-2598; Appendino, G., Bertolino, A., Minassi, A., Annunziata, R., Szallasi, A., de Petrocellis, L., Di Marzo, V. *Eur. J. Org. Chem.* **2004**, 3413-3421.



Scheme 99 Proposed Mechanism for the Formation of s81 in the Presence of MsCl

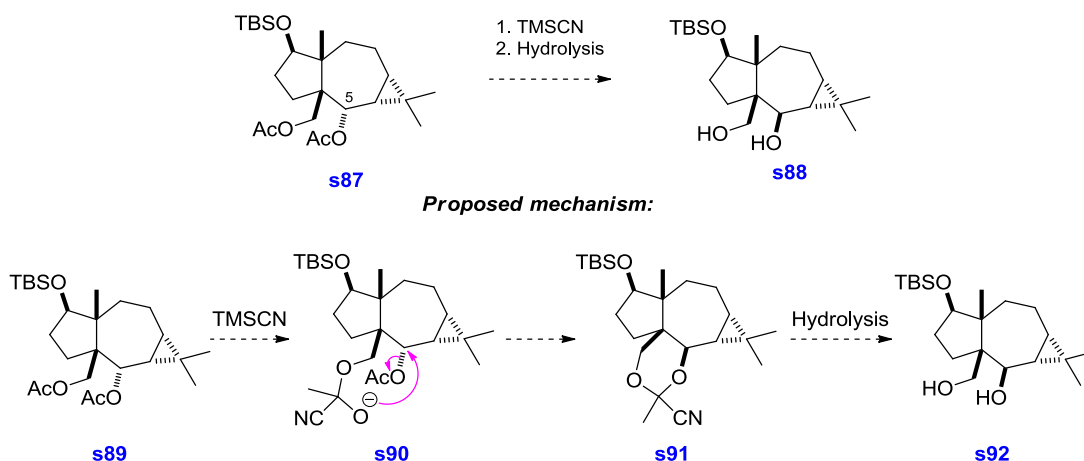
To try and avoid the E_2 elimination pathway, and see whether the opening reaction could be avoided, **s69** was transformed into its TMS-protected form (*Scheme 100*, **s85**) but once again, only the formation of the diene compound resulting from the opening of the cyclopropane was observed (*Scheme 100*, **s86**). The latter product was formed in 15% yield, along with 85% of recovered starting material. Thus, it seems that a leaving group could not be formed in position 5 without the opening of the cyclopropane to occur *via* an E_1 elimination pathway. It is worth noting that this is somewhat contradictory with the mechanism proposal of Barnekow and Cardellina for the biosynthesis of (-)-Neomeranol.



Scheme 100 Protection of the Primary Alcohol of s69 into its TMS Derivative and Attempt toward the Mesylation of the Secondary Alcohol in Position 5

c) Formation of an Acetal

A 1,3-bis acetate compound can be transformed into an acetal by the addition of TMSCN followed by nucleophilic substitution of one of the two acetates.¹⁷² Then, hydrolysis of the acetal delivers the expected product with the two alcohols in a *cis* relationship.



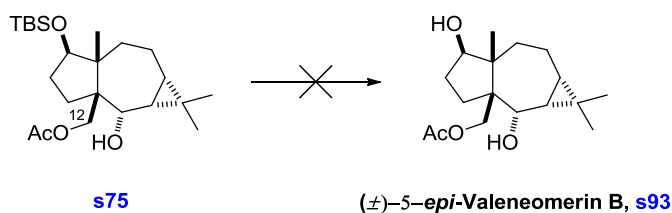
Scheme 101 Inversion of Configuration Envisioned via the Formation of an Acetal s91

In order to investigate this strategy, preparation of the bis acetate compound **s89** was attempted. But surprisingly, only the acetylation of the primary alcohol occurred. Even in the presence of excess acetic anhydride at reflux of dichloroethane for a long period of time (24 h), the secondary alcohol remained free.

4. Total Synthesis of (\pm)-5-*epi*-Valeneomerin B **s93**

Since the inversion of the alcohol (in position 5) has not been successful yet, we did consider the synthesis of (\pm)-5-*epi*-Valeneomerin B. For this purpose, the deprotection of **s75** was required but surprisingly, no reaction occurred either with TBAF or HF.pyridine when the alcohol in position 12 was acylated (*Table 28*).

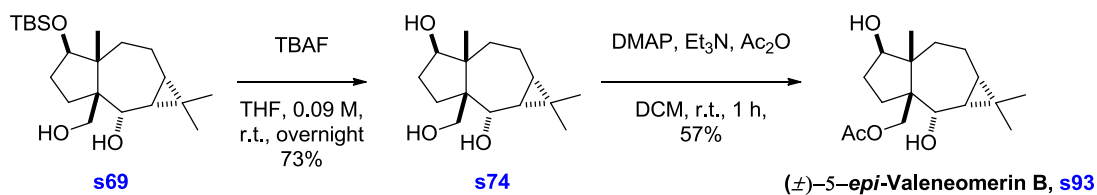
¹⁷² Noheda Marin, P., Tabares Cantero, N., Benito Arenas, R., Hojas Garcia, E., Maroto Quintana, S. *PTC Int. Appl.* **2008**, WO 2008098916 A1 20080821.



Entry	Reagent	Reaction conditions	Outcome
1	TBAF	THF, 0,09 M, r.t., overnight	No reaction
2	HF.pyridine	THF, r.t., overnight	No reaction

Table 27 Attempts toward the Deprotection of **s75**

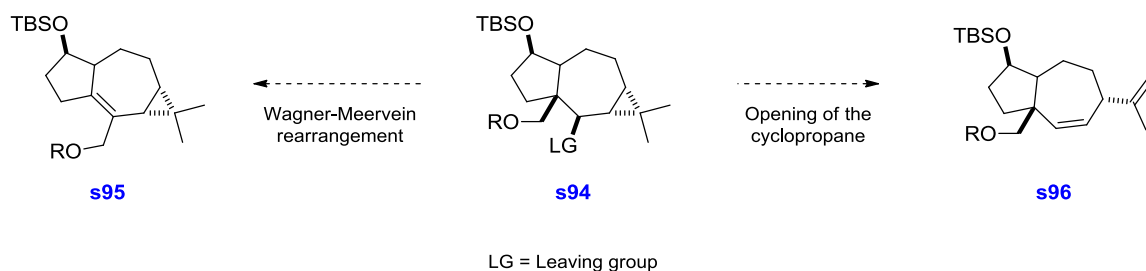
The deprotection of **s69**, however, was successful, with triol **s74** being formed in 73% yield. Then, the selective acylation of the primary alcohol (in position 12) afforded (\pm)-5-*epi*-Valeneomerin B **s93** in 57% yield. Thus, the first fully diastereoselective total synthesis of (\pm)-5-*epi*-Valeneomerin B was completed in 5% overall yield over 13 steps (*Scheme 102*).



Scheme 102 Completion of the Synthesis of (\pm)-5-*epi*-Valeneomerin B **s93**

5. Conclusion and Perspectives

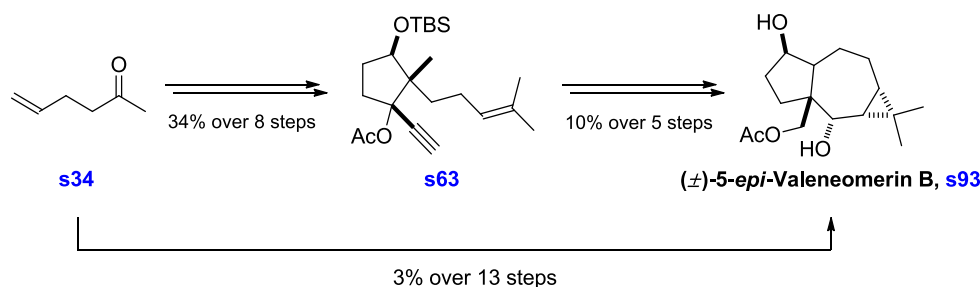
The alkoxy methylation of **s64** was successfully achieved. However, the diastereoselective reduction of the resulting ketone furnished the wrong diastereomer, most likely for steric reasons. Furthermore, the inversion of the alcohol so formed is challenging because the formation of a leaving group in α -position to a cyclopropane and a neopentyl centre (*Scheme 103*, **s94**) is prone to trigger either a Wagner-Meerwein rearrangement or the opening of the cyclopropane *via* an E_1 -type elimination pathway (*Scheme 103*).



Scheme 103 Plausible Wagner-Meerwein Rearrangement (Left) and Opening of the Cyclopropane (Right) that Would Arise from the E_1 -Type Elimination of the Leaving Group

Of note, α -cyclopropyl radicals undergo fast cyclopropane opening, so that dissolving metal reductions are not likely to work either.

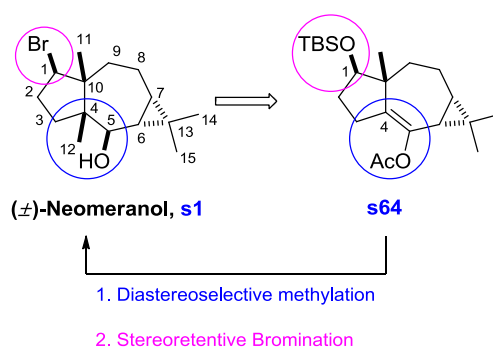
Nevertheless, the total synthesis of (\pm)-5-*epi*-Valeneomerin B was completed in 3% yield over 13 steps (*Scheme 104*). Biological testing of the latter compound is under way.



*Scheme 104 Total Synthesis of (\pm)-5-*epi*-Valeneomerin B s93*

IV. Studies toward the Total Synthesis of (\pm)-Neomeranol

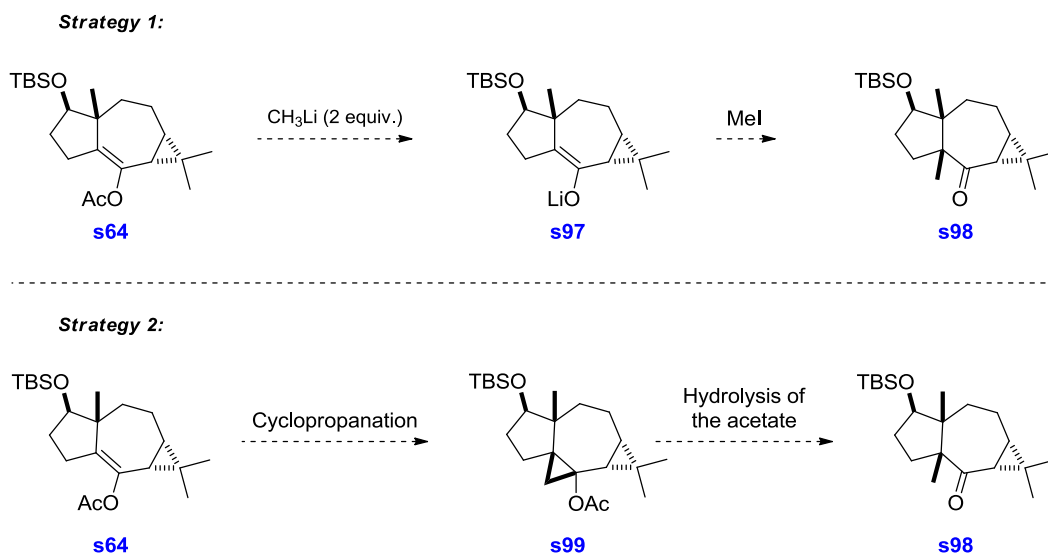
Cyclized intermediate **s64** resulting from the gold-catalyzed propargyl acetate rearrangement is also a precursor of (\pm)-Neomeranol. For the natural product to be obtained, the introduction of a methyl group in position 4 was required, as well as the bromination of position 1. To avoid elimination or reduction issues inherent to the presence of a bromine atom in the structure, the alkylation should be considered before the bromination (*Scheme 105*). Here are presented independently conducted studies toward the diastereoselective methylation and stereoretentive bromination of **s64**.



*Scheme 105 Retrosynthetic Analysis (Upper Part) and Synthetic Planning (Bottom Part) of (±)-Neomeranol **s1***

1. Methylation

Two different strategies may be considered when it comes to the stereoselective methylation of enol acetate **s64**. On the one hand, the latter may be exploited as a precursor for the corresponding enolate **s97**, as previously in the alkoxymethylation reaction (*Scheme 106*, upper part). On the other hand, the stereoselective cyclopropanation of the enol acetate followed by hydrolysis may be envisioned (*Scheme 106*, bottom part).



*Scheme 106 Strategies Envisioned toward the Diastereoselective Methylation of **s64***

a) Via Cyclopropanation

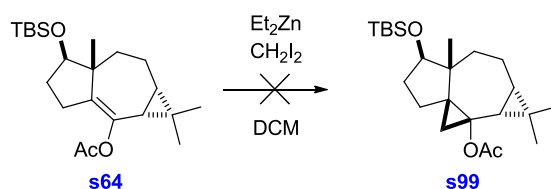
The cyclopropanation–hydrolysis strategy should be both more regio- and stereoselective than alkylation of the lithium enolate **s97**. A well-known cyclopropanation reaction is the Simmons-Smith reaction, which uses iodomethyl zinc reagents. Various procedures were reported for the generation of the latter, namely:

-the oxidative addition of a dihalomethane to zinc metal, as in the original Simmons–Smith procedure;¹⁷³

-the reaction of a zinc(II) salt with a diazoalkane, first reported by Wittig and co-workers;¹⁷⁴

-or an alkyl exchange reaction between an alkyl zinc and a 1,1- dihaloalkane, often referred to as the Furukawa procedure and originally reported in 1966.¹⁷⁵

The latter halomethylzinc generation involves the treatment of a solution of Et₂Zn with CH₂I₂. The use of a 2:1 ratio of CH₂I₂ to Et₂Zn generates (ICH₂)₂Zn,¹⁷⁶ while a 1:1 ratio presumably generates EtZnCH₂I.³⁴ Although the reaction is generally most successful with electron-rich alkenes, the cyclopropanation of alkenes ranging from electron rich to electron deficient has been achieved.¹⁷⁷ Especially, there are some reports of the cyclopropanation of vinyl acetates.¹⁷⁸ Of note, a strong accelerating and stereodirecting effect of oxygen functions proximal to the alkene has been noticed. It is also worth mentioning that the addition of CF₃CO₂H (TFA) to Et₂Zn and CH₂I₂ generates a reagent (presumably CF₃COOZnCH₂I) that is particularly effective for the cyclopropanation of less reactive alkenes.¹⁷⁹ Unfortunately, no reaction occurred, either in the presence of 1 or 2 equivalents of CH₂I₂ relative to ZnEt₂ (*Table 28, entries 1-2*), even when TFA was added (*Table 28, entries 2-3*). Elevated temperature and prolonged reaction time were not beneficial to the reaction (*Table 28, entry 3*). The unsuccess of the reaction may be due to strong steric hindrance together with the electron deficiency of the alkene.



¹⁷³ Simmons, H.E., Smith, R.D. *J. Am. Chem. Soc.* **1958**, *80*, 5323; Simmons, H.E., Smith, R.D. *J. Am. Chem. Soc.* **1959**, *81*, 4256. This reagent was first prepared by Emschwiler: Emschwiler, G. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1929**, 188, 1555.

¹⁷⁴ Wittig, G., Schwarzenbach, K. *Angew. Chem* **1959**, *71*, 652; Wittig, G., Schwarzenbach, K. *Justus Liebigs Ann. Chem.* **1962**, 650, 1; Wittig, G., Wingler, F. *Justus Liebigs Ann. Chem.* **1962**, 656, 18; Wittig, G., Wingler, F. *Chem. Ber.* **1964**, *97*, 2146; Wittig, G., Jautelat, M. *Justus Liebigs Ann. Chem.* **1967**, 702, 24.

¹⁷⁵ Furukawa, J., Kawabata, N., Nishimura, J. *Tetrahedron Lett.* **1966**, 3353; Furukawa, J., Kawabata, N., Nishimura, J. *Tetrahedron* **1968**, *24*, 53; Nishimura, J., Furukawa, J., Kawabata, N., Kitayama, M. *Tetrahedron* **1971**, *27*, 1799.

¹⁷⁶ Denmark, S.E., Edwards, J.P., Wilson, S.R. *J. Am. Chem. Soc.* **1991**, *113*, 723; Denmark, S.E., Edwards, J.P., Wilson, S.R. *J. Am. Chem. Soc.* **1992**, *114*, 2592.

¹⁷⁷ Simmons, H.E., Cairns, T.L., Vladuchick, S.A., Hoiness, C.M. *Org. React.* **1972**, *20*, 1.

¹⁷⁸ Morisson, V., Barnier, J.P., Blanco, L. *Tetrahedron* **1998**, *54*, 7749-7764.

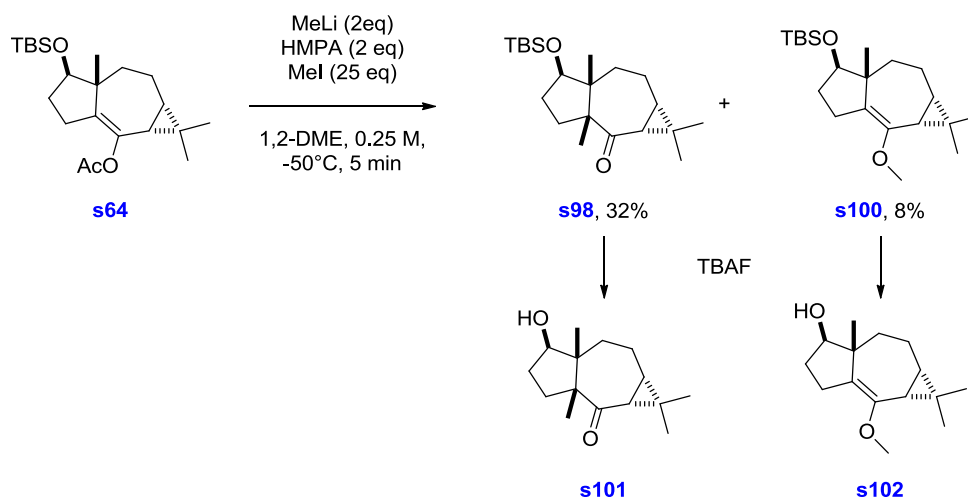
¹⁷⁹ Yang, Z.Q., Lorenz, J.C., Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621.

Entry	Neq Et ₂ Zn	Neq CH ₂ I ₂	Concentration	Temperature and reaction time	TFA	Outcome
1 ¹⁵⁷	1.1	1.1	Neat	r.t., 2 h	-	No reaction
2	2	4	0.5 M	0°C, 4 h	2 eq	No reaction
2	2	4	0.5 M	r.t., overnight	2 eq	No reaction

Table 28 Attempts for the Cyclopropanation of Enol Acetate **s64**

b) Via Alkylation of an Enolate

Cyclized intermediate **s64** was reacted in the conditions reported by House and Trost.²³ Worthy of note, MeI required to be dried over CaH₂ and freshly distilled for the reaction to occur. Although not mentioned by House and Trost, O-alkylation issues were encountered. More specifically, a moderate yield of a 4:1 mixture of C- and O-alkylation products **s98** and **s100** was obtained, the characterization of which was made possible by removal of the TBS protecting-group in the presence of TBAF. Unfortunately, the reaction could not be optimized further by carefully controlling the rate of addition of MeLi or the temperature of the reaction. The presence or absence of HMPA did not have any impact on the reaction outcome either (*Scheme 108*). The addition of ZnCl₂ to the reaction mixture to form the zinc enolate, however, should prevent the O-alkylation pathway.

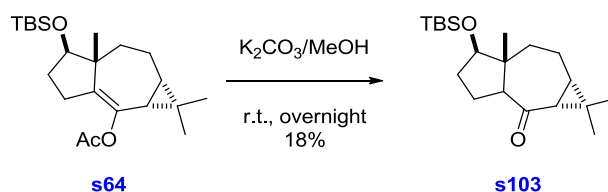


Scheme 107 Attempt for the Selective Methylation of the Enol Acetate Derivative **s64**

Alternatively, the lithium enolate may be formed from the hydrolysis derivative of **s64**. Rigby and co-workers indeed showed that such an enol acetate can be cleaved with K₂CO₃/MeOH to provide the corresponding ketone in excellent yields.¹⁸⁰ Unfortunately, these

¹⁸⁰ Rigby, J.H., Senanayaki, C. *J. Org. Chem.* **1988**, 53, 440-443.

conditions furnished ketone **s41** in low yields, so that this strategy was not valuable (*Scheme 109*).

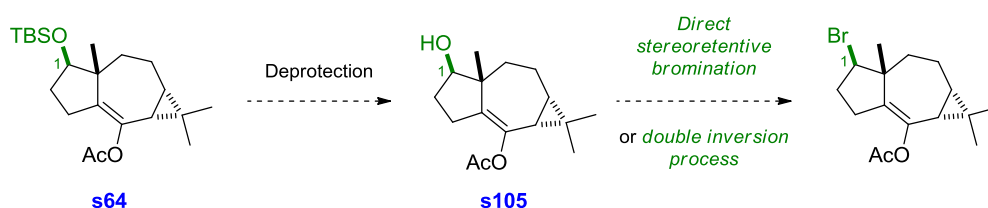


Scheme 108 Attempt for the Hydrolysis of Enol Acetate s64 with $\text{K}_2\text{CO}_3/\text{MeOH}$

2. Studies toward the Bromination

a) Stereoretentive Bromination

After deprotection of **s64**, stereoretentive bromination at position **1** may be achieved either directly, or indirectly *via* a double inversion process (*Scheme 110*).



Scheme 109 Direct Stereoretentive Bromination of s64 at Position 1 or double Inversion Process toward the Total Synthesis of (±)-Neomeranol s1

In 2008, Lepore and co-workers reported stereoretentive halogenations and azidations with titanium (IV) enabled by chelating leaving groups.¹⁸¹ Their strategy to increase the likelihood of a frontside attack (stereoretentive bromination requires a frontside attack) was based on the minimization of the charge repulsion between the leaving group and the nucleophile, and was achieved using Lewis acids containing nucleophilic ligands. The Lewis acid is expected to diminish the partial negative charge in the leaving group through chelating interactions and at the same time, to deliver its nucleophilic ligand to the substrate from the front face (*Figure 4*, $\text{S}_{\text{N}}\text{i}$ mechanism). A possible transition state was proposed, that involves a stable six-membered ring geometry with the quinsylate nitrogen coordinated to titanium IV.

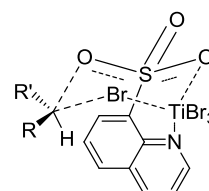
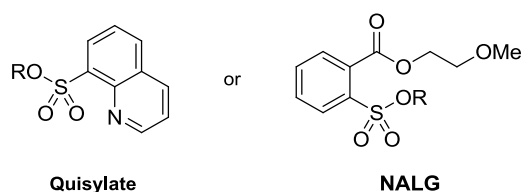


Figure 4 Possible Transition State for the stereoretentive Bromination with TiBr_4

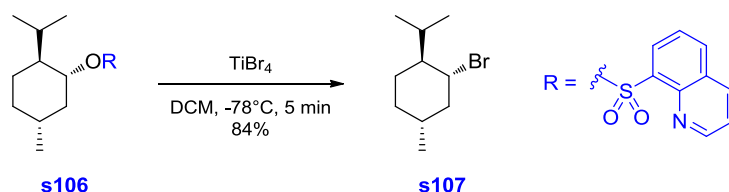
¹⁸¹ Lepore, S.D., Mondal, D., Li, S.Y., Bhunia, A.K. *Angew. Chem. Int. Ed.* **2008**, 47, 1-5.

The scope of the reaction was shown to be broad: chlorination, bromination, iodination and azidation of secondary alkyl sulfonates all performed well. This strategy was made possible by the utilization of new alkyl sulfonate-based leaving groups, namely 8-quinoline sulfonate (quisylate, *Scheme 111*, left) or diethylene oxide containing nucleophile-assisting leaving groups (NALGs, *Scheme 111*, right).



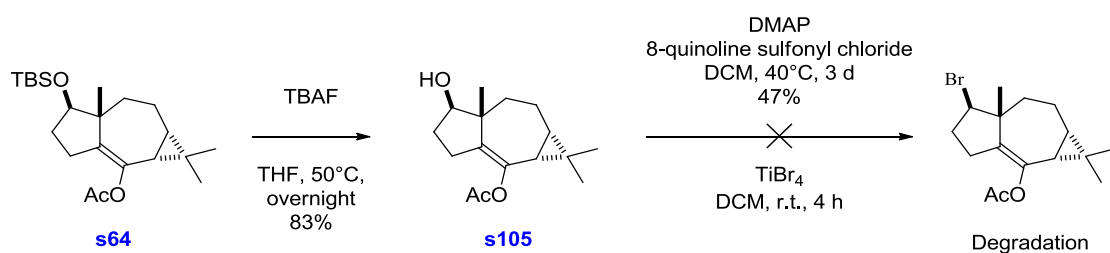
Scheme 110 Generality for stereoretentive Halogenation and Azidation

In particular, the bromination of challenging substrates could be achieved using this method. For instance, menthyl quisylate reacted with TiBr_4 to give the corresponding menthyl bromide product in 84% yield after a 5 min-reaction at -78°C in dichloromethane (*Scheme 112*).



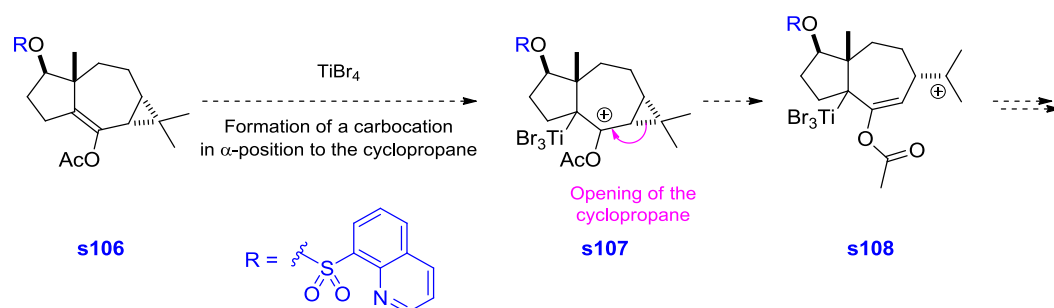
Scheme 111 Stereoretentive Bromination of menthyl Quisylate s106

For the latter strategy to be applied to the total synthesis of (\pm)-Neomeranol, the TBS protecting group was removed at this stage (*Scheme 113*). TBAF was used for this purpose, and the expected product was obtained in 83% yield. 8-quinoline sulfonyl chloride is commercially available. For this reason, the quisylate leaving group rather than the NALG was selected for the testing of the stereoretentive bromination. Thus, the quisylate intermediate was prepared in the presence of DMAP and 8-quinoline sulfonyl chloride. Though the reaction was very sluggish and the yield moderate (47%), the expected product was formed, which was directly engaged into the bromination step. Unfortunately, no reaction occurred, neither under the conditions reported by Lepore (-78°C) nor at 0°C . In contrast, complete degradation of the starting material was encountered when the reaction was run at room temperature (*Scheme 107*).



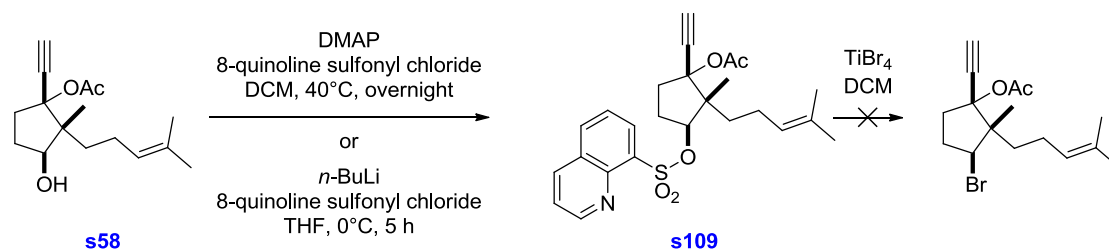
Scheme 112 Removal of the TBS Protecting group with TBAF and Attempt for the retentive Bromination with TiBr_4

A possible reason for the failure of the procedure may be the preferential coordination of TiBr_4 to the vinyl acetate instead of the quinsylate (most likely for steric reasons), which might induce the formation of a carbocation in α position to the cyclopropane (*Scheme 114*, **s107**), thus leading to the opening of the latter (*Scheme 114*, **s108**).



Scheme 113 Possible Side Reaction in the Presence of TiBr_4

Alternatively, the bromination could be performed prior to cyclization. Once again, the quinsylate intermediate **s109** was formed in moderate yield (52%), whatever the procedure used, and engaged directly into the bromination step (*Table 29*). Unfortunately, none of the expected bromide derivative could be isolated from the reaction of this substrate with TiBr_4 either. No reaction occurred at low temperature ($-78^\circ\text{C} < T < 0^\circ\text{C}$). On the contrary, running the reaction at room temperature led to complete degradation of the starting material. Once again, TiBr_4 is a powerful Lewis acid, which may activate the propargyl acetate or the alkene and lead to undesired reactions (eliminations, nucleophilic additions...).

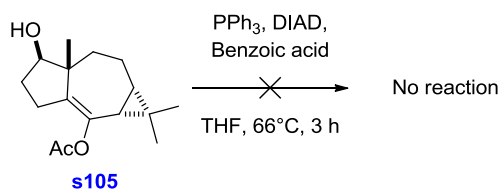


Entry	Conditions	Yields
1	DMAP 8-quinoline sulfonyl chloride DCM, 40°C, overnight	52%
2	<i>n</i> -BuLi 8-quinoline sulfonyl chloride THF, 0°C, 5 h	52%

Table 29 Preparation of the Quisylate Intermediate for Bromination Prior to Cyclization

b) Double Inversion of Configuration via a Mitsunobu Reaction

A Mitsunobu protocol was investigated, to probe the feasibility of a double inversion. The reaction, run with benzoic acid and DIAD, was regrettably not successful. Yet, the reaction is known to be sensitive to steric hindrance (Scheme 115).

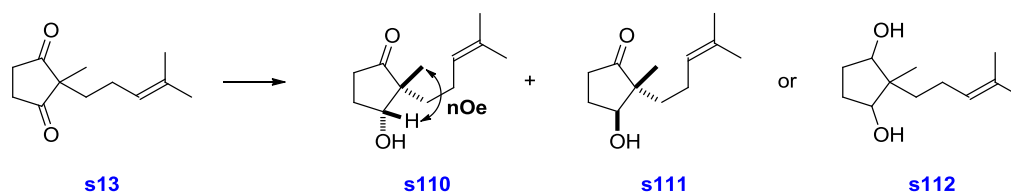


Scheme 114 Attempt for Mitsunobu Inversion

c) Modification of the Retrosynthetic Scheme

Following these results, the strategy was modified so that the bromination could occur with inversion of configuration. To do so, the diastereoselectivity of the ketone reduction needed to be reversed. Because acetate and alcohol functions did act as directing groups, the reduction should be performed prior to the 1,2-addition of TMSA (Table 30). Various reducing agents were tested but the reaction could not be performed with a complete control of the diastereoselectivity as it was the case in the 1,2-addition of TMSA, due to the little difference there is, from a steric point of view, between methyl and methylene groups. L-selectride gave a complex mixture from which no characterizable compound could be isolated (Table 30, entry 3). Luche conditions furnished the diol compound (Table 30, entry 2). The best result was obtained

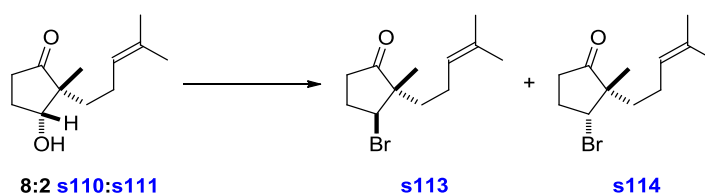
with $\text{LiAlH}(\text{OtBu})_3$ as the reducing agent (*Table 30, entry 1*). A 81:19 mixture of diastereomer was obtained that could not be separated at this stage. Of note, running the reaction at -20°C afforded the same diastereomeric ratio. (81:19 **s110:s111**). The diastereoselectivity of the reaction was determined by Noesy. A correlation between the proton in α to the hydroxyl group and the methyl substituent indicated a *cis* relationship between them.



Entry	Reducing agent	Reaction conditions	Conversion	Isolated Yields	s110:s111 ratio:
1	$\text{LiAlH}(\text{OtBu})_3$	THF, 0°C , 2 h	Total	92% s110 + s111	81:19
2	NaBH_4 , $\text{CeCl}_3 \cdot 7 \text{H}_2\text{O}$	MeOH, -10°C , 5 min	Total	33% s112	-
3	L-selectride	THF, 0°C , 2 h	Total	Complex mixture	
4	(R)-(+)-2-Methyl-CBS oxazolidine solution	THF	83%	32% s110 + s111	76:24

Table 30 Optimization of the Diketone Desymmetrization via Reduction

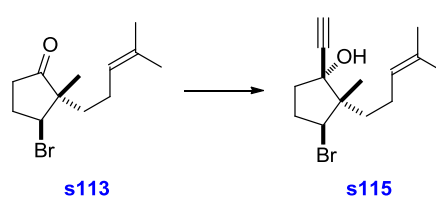
The bromination was first attempted in the presence of PBr_3 in THF. But this resulted in the complete degradation of the starting material. The use of PPh_3 and CBr_4 however afforded the diastereomeric products **s113** and **s114**, that can be separated by chromatography (*Table 31, entry 2*).



Entry	Reaction conditions	Outcome
1	PBr_3 THF, r.t., overnight	Degradation
2	PPh_3 , CBr_4 THF, 0°C , 1 h	56%

Table 31 Optimization of the Bromination Step

Then, the introduction of the alkyne moiety was envisioned. Several issues were to be faced. Firstly, the reagent used had not to be basic enough for the elimination of bromine atom to occur. Secondly, the diastereoselectivity of the reaction might be different than with the diketone precursor, so that novel optimization might be required. The optimal conditions described previously were attempted but only half conversion was reached (*Table 32, entry 1*).¹⁸² In the absence of CeCl₃, no reaction occurred (*Table 32, entry 2*) but the combination of ethynylmagnesium bromide and anhydrous CeCl₃ led to total conversion (*Table 32, entry 3*). The expected product **s115** was obtained in 83% yield and a single diastereomer was obtained. Of note, replacing TMSA by ethynylmagnesium bromide allows to suppression the deprotection step, in which the bromine atom might undergo undesired elimination.

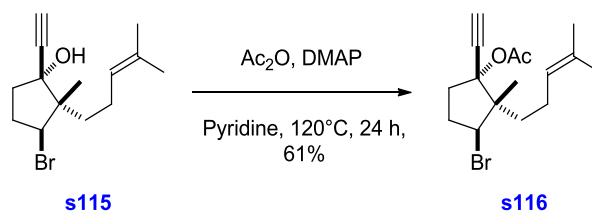


Entry	Reagent	Neq CeCl ₃	Reaction conditions	Conversion	Yields
1	TMSA, <i>n</i> -BuLi	3.5	THF, -78°C -> r.t., overnight	48%	-
2	EthynylMgBr	0	THF, -78°C	No reaction	
4	EthynylMgBr	7	THF, -78°C, -78°C -> r.t., overnight	Total	83%

Table 32 Optimization of the 1,2-acetylide addition to s113

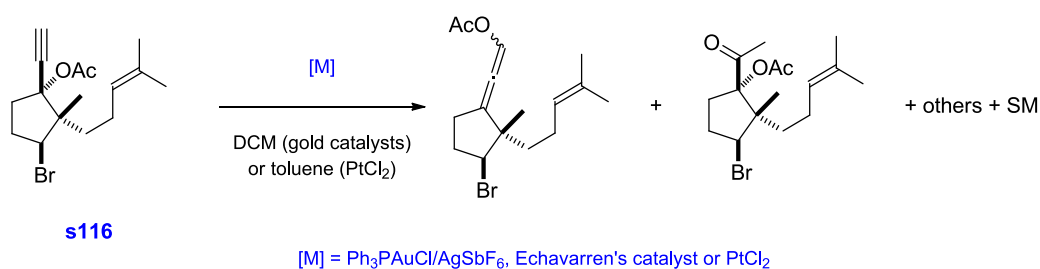
The enolate anion resulting from the 1,2-addition of ethynylmagnesium bromide in the presence of CeCl₃ was quenched with Ac₂O. This unfortunately did not yield the acetate derivative, even in the presence of a large excess of acetic anhydride, DMAP and elevated temperature for several hours. The inertia of the cerium enolate might be due the pronounced oxophilicity of cerium. Consequently, the propargyl alcohol **s115** was isolated before being acylated. In order for the elimination of the bromine atom not to occur, the use of the somewhat basic DMAP was avoided at first, so that the reaction was run in pyridine. The addition of DMAP was nevertheless required for the reaction to be complete. Fortunately, the elimination of the bromine atom was not observed and the expected product **s116** could be isolated in 61% yield (*Scheme 115*).

¹⁸² Most probably due to the poor quality of the reagent used.



Scheme 115 Acetylation of Propargyl Alcohol s115

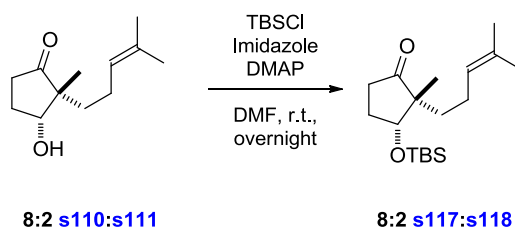
Gold-catalyzed reactions involving halogenated substrates have been reported in the literature,¹⁸³ so that it was envisaged with confidence that the bromide derivative **s116** would react under these conditions. Under gold or platinum catalysis, unfortunately, a complex mixture among which the allenyl acetate, the product resulting from the hydration of the triple bond and unreacted starting material were observed (*Scheme 116*). It seems that the reaction is blocked in the presence of the bromide derivative. This means the bromination, either stereoretentive or not, has to be performed after the cyclization step.



Scheme 116 Attempts toward the Metal-catalyzed Propargyl Acetate Rearrangement and Subsequent Intramolecular Cyclopropanation of s116

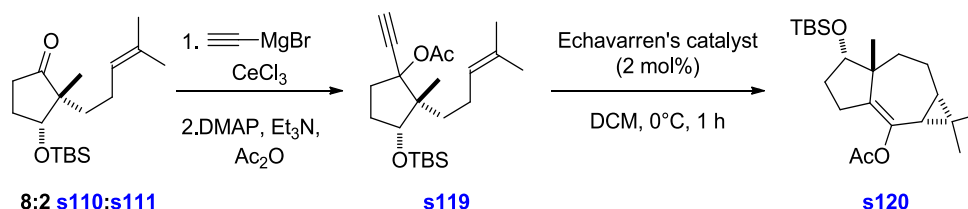
One strategy to explore was the protection of propargyl alcohol **s110** into its TBS derivative so that the bromination would be performed after the cyclization step, with inversion of the configuration. Yet the bromination was required for both diastereomers **s110** and **s111** to be separated. Protection of **s110** into its TBS derivative could indeed be performed without any difficulty but both diastereomers **s117** and **s118** remained inseparable (*Scheme 117*).

¹⁸³ For examples, see: Staben, S.T., Kennedy-Smith, J.J., Huang, D., Corkey, B.K., LaLonde, R.L., Toste, F.D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671-7673; Huwyler, N., Carreira, E.M. *Angew. Chem. Int. Ed.* **2012**, *51*, 13066-13069.



Scheme 117 Protection of the Diastereomeric Alcohols s110 and s111 into their TBS Derivatives s117 and s118

Unfortunately, the 1,2-acetylide addition was not stereoselective in this case, so that a complex mixture of four diastereomers was obtained (*Scheme 118*). There might be a steric clash between the large TBS group and cerium, resulting in a less diastereoselective 1,2 addition. Moreover, the smaller ethynylmagnesium bromide was used instead of TMSA in this case. One of the four diastereomers, however, could be separated from the reaction mixture after acylation (the *trans* relationship between the TBS-protected alcohol and the methyl group was determined by a Noesy experiment), and tested into the metal-catalyzed rearrangement step (*Scheme 118*). It seems that the diastereoselectivity of the starting material did not impact the selectivity of the reaction. However, **s120** was more difficult to isolate from the reaction mixture than its diastereomeric counterpart **s64**. Overall, this was not a viable strategy toward (\pm)-Neomeranol.



Scheme 118 Attempts for the Preparation and Cyclization of s119

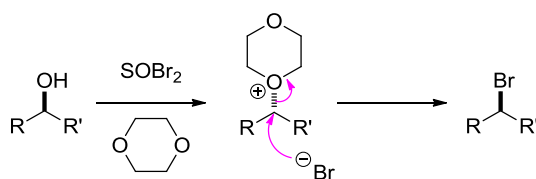
3. Conclusion and Perspectives

As mentioned earlier, the methylation of enol acetate **s64** and subsequent reduction of the resulting ketone should be considered before bromination to avoid elimination and reduction issues. Selective C-methylation of **s64** may be achieved *via* the *in situ* formation of a zinc enolate.

It is likely that the same selectivity issues than in the total synthesis of (\pm)-Valeneomerin B are going to be encountered in the reduction of the newly formed ketone.

To achieve stereoselective bromination, the protection of the resulting alcohol in position 5 may be required. Because TiBr_4 is a strong Lewis acid, which may trigger cyclopropane

opening, its use should be avoided. Alternatively, it could be replaced with KBr, NaBr or even LiBr, although the reaction may require higher temperatures to proceed. Otherwise, we may envision a double inversion process. Treatment of an alcohol with SOBr_2 affords the corresponding alcohol with inversion of the configuration. However, the bromination may occur with inversion of the configuration when run in a nucleophilic solvent such as dioxane (Scheme 119). Yet, it is very likely that a mixture of diastereomers is going to be obtained. In addition, an E_1 -type elimination of the leaving group would most probably trigger a Wagner-Meerwein rearrangement.



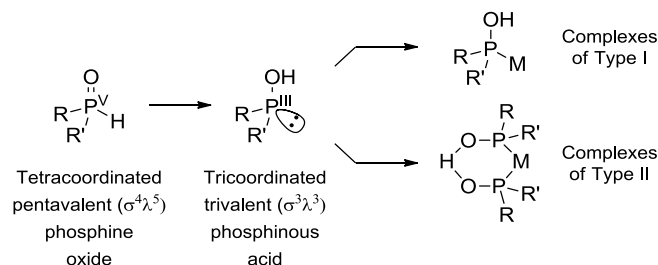
Scheme 119 Stereoretentive Bromination via a Double Inversion Process in Dioxane

Chapter II

Preparation and Application in Catalysis of Secondary Phosphine Oxide–Gold(I) Complexes

I. Introduction

Secondary phosphine oxides (SPOs) have been widely used for the synthesis of tertiary phosphine oxides and found applications as Wittig Horner reagents¹⁸⁴. In 1968, Chatt and Heaton reported that in solution, there exists a tautomeric equilibrium between the tetracoordinated pentavalent ($\sigma^4\lambda^5$) phosphine oxide form $RR'P(O)H$ and the tricoordinated trivalent ($\sigma^3\lambda^3$) phosphinous acid form $RR'P(OH)$, which equilibrium is generally completely shifted towards the phosphine oxide form but can nevertheless be displaced in favour of the $P^{(III)}$ compound by coordination to transition metals (Scheme 120).¹⁸⁵ Worthy of note, the coordinated phosphinous acids are weak acids that can be deprotonated to afford the corresponding anionic phosphinito ligands so that in the presence of a base, complexes of type II can be formed, in which a phosphinous acid and a phosphinito ligand are in a *cis* relationship and strongly linked through a hydrogen bond, thus together acting similarly to a bidentate ligand (Scheme 120).¹⁸⁶



Scheme 120 Coordination of SPOs to Metals

Accordingly, SPOs have later been used as effective ligands for transition-metal complexes, especially with palladium, but also to a lesser extent with nickel, ruthenium, rhodium and platinum.¹⁸⁷ For example, the catalytic system generated *in situ* from $[Pd_2(dba)_3]$ and $tBu_2P(O)H$ efficiently catalyses the Suzuki-Miyaura cross coupling between 4-chloroanisole and

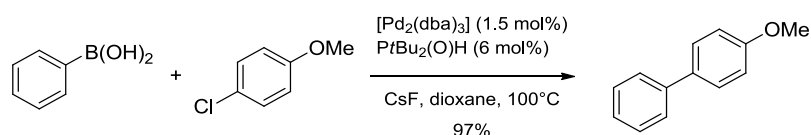
¹⁸⁴ Bhattacharya, A.K., Roy, N.K. “Methods of Preparation of Phosphine Chalcogenides” in *The Chemistry of Organophosphorous Compounds* **1992**, Vol. 2 (Ed.: F.R. Hartley), Wiley Chichester, 195-285; R.S. Edmundson “Chemical Properties and Reactions of Phosphine Chalcogenides” in *The Chemistry of Organophosphorous Compounds* **1992**, Vol. 2 (Ed.: F.R. Hartley), Wiley Chichester, 287-407.

¹⁸⁵ Chatt, J., Heaton, B.T. *J. Chem. Soc. (A)* **1968**, 2745-2757.

¹⁸⁶ Achard, T., Giordano, L., Tenaglia, A., Gimbert, Y., Buono, G. *Organometallics* **2010**, 29, 3936-3950.

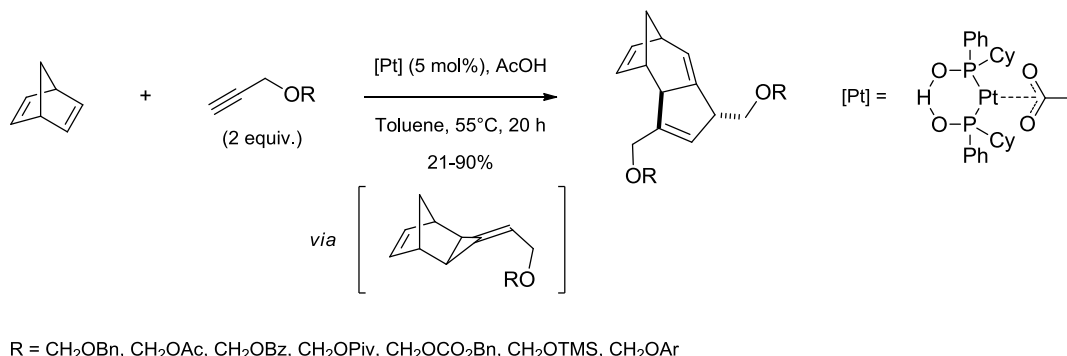
¹⁸⁷ Roudhill, D.M., Sperline, R.P., Beaulieu, W.B. *Coord. Chem. Rev.* **1978**, 26, 263-279; Walther, B. *Coord. Chem. Rev.* **2002**, 235, 121-140.

boronic acid (Scheme 121).¹⁸⁸ Notably, various C-C, C-N and C-S bonds could be formed by this method using unactivated aryl chlorides as partners. Subsequently, various other cross coupling reactions were investigated, mostly by the groups of Li, Wolf and Ackermann.¹⁸⁹ Though effective as well for cross coupling reactions, nickel and ruthenium have been far less investigated than palladium. However, phosphinous acid-ruthenium complexes have revealed competent for the activation of C-H bonds.¹⁹⁰



Scheme 121 Suzuki-Miyaura Cross Coupling between 4-Chloroanisole and Boronic Acid with *t*Bu₂P(O)H as the Ligand for Palladium

Along with cross coupling and C-H activation reactions, SPOs allowed the development of unprecedented transformations. Buono and co-workers for instance reported a regio- and diastereoselective platinum-catalyzed intermolecular tandem [2+1]/[3+2] cycloadditions sequence,¹⁹¹ which reaction is not observed when other metal complexes or ligands are used (Scheme 122).



Scheme 122 Intermolecular Tandem [2+1]/[3+2] Cycloadditions Sequence Catalyzed by a SPO-Pt Complex of Type II

Of note, the phosphorus atom of SPOs can be stereogenic, and some efforts have indeed been made in their enantioselective synthesis.¹⁹² Yet, the successful applications in catalysis

¹⁸⁸ Li, G.Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 1513-1516.

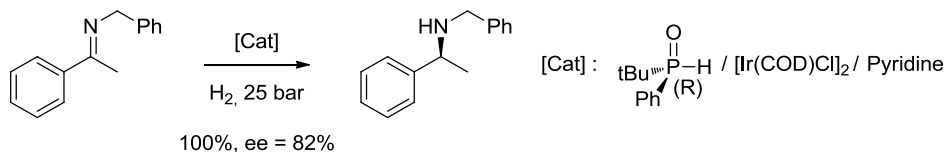
¹⁸⁹ For reviews see: Dubrovina, N.V., Börner, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5883-5886; Ackermann, L. *Synthesis* **2006**, *10*, 1557-1571; Ackermann, L. *Synlett* **2007**, *4*, 507-526; Ackermann, L. *Isr. J. Chem.* **2010**, *50*, 652-663; Shaikh, T.M., Weng, C.-M., Hong, F.-E. *Coord. Chem. Rev.* **2012**, *256*, 771-803.

¹⁹⁰ Ackermann, L. *Org. Lett.* **2005**, *7*, 3123-3125; Ackermann, L., Althammer, A., Born, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 2619-2622; Ackermann, L., Lygin, A.V. *Org. Lett.* **2011**, *13*, 3332-3335.

¹⁹¹ Achard, T., Lepronier, A., Gimbert, Y., Clavier, H., Giordano, L., Tenaglia, A., Buono, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 3552-3556.

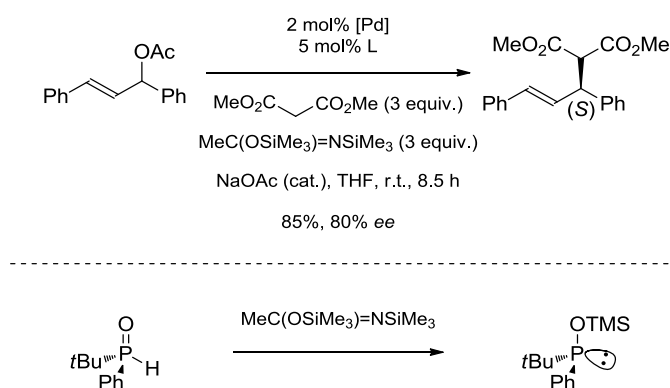
¹⁹² Dubrovina, N.V., Börner, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5883-5886.

remain scarce besides iridium- and rhodium-catalyzed hydrogenations pioneered by Minnaard, Feringa and de Vries, where enantiomeric excesses up to 99% were reached (*Scheme 123*).¹⁹³



Scheme 123 Iridium-catalyzed Asymmetric Hydrogenation

The asymmetric version of the [2+1] cycloaddition developed by Buono and the palladium-mediated asymmetric allylic alkylation reported by the group of Dai (*Scheme 124*, upper part) deserve mention.¹⁹⁴ In this latter case, it was later demonstrated by Nemoto and Hamada that the chiral ligand is actually the TMS-protected phosphinous acid (*Scheme 124*, bottom part).¹⁹⁵



Scheme 124 Palladium-Mediated Asymmetric Allylic Alkylation (Upper Part) and Formation of a TMS-Protected Phosphinous Acid in the Presence of Bis(trimethylsilyl)acetamide (Lower Part)

SPO-Au(I) complexes were described by Chicote and Jones¹⁹⁶ and Schmidbaur¹⁹⁷. Only coordination and structural studies were nonetheless performed. For instance, ligand exchange

¹⁹³ Jiang, X.-B., Minnaard, A.J., Hessen, B., Feringa, B.L., Duchateau, A.L.L., Adrien, J.G.O., Boogers, J.A.F., de Vries, J.G. *Org. Lett.* **2003**, *5*, 1503-1506; Jiang, X.-B., van den Berg, M., Minnaard, A.J., Feringa, B.L., de Vries, J.G. *Tetrahedron: Asymmetry* **2004**, *15*, 2223-2229; Landert, H., Spindler, F., Wyss, A., Blaser, H.-U., Pugin, B., Ribourduoille, Y., Gschwend, B., Ramalingam, B., Pfaltz, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 6873-6876; Liniger, M., Gschwend, B., Neuburger, M., Schaffner, S., Pfaltz, A. *Organometallics* **2010**, *29*, 5953-5958.

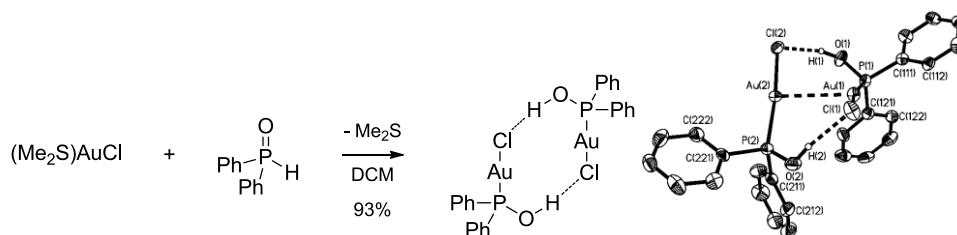
¹⁹⁴ Gatineau, D., Moraleda, D., Naubron, J.-V., Bürgi, T., Giordano, L., Buono, G. *Tetrahedron: Asymmetry* **2009**, *20*, 1912-1917.

¹⁹⁵ Dai, W.-M., Yeung, K.K.Y., Leung, W.H., Haynes, R.K. *Tetrahedron: Asymmetry* **2003**, *14*, 2821-2826; Nemoto, T., Hamada, Y. *Chem. Rec.* **2007**, *7*, 150-158.

¹⁹⁶ Vicente, J., Chicote, M.T., Jones, P.G. *Inorg. Chem.* **1993**, *32*, 4960-4964.

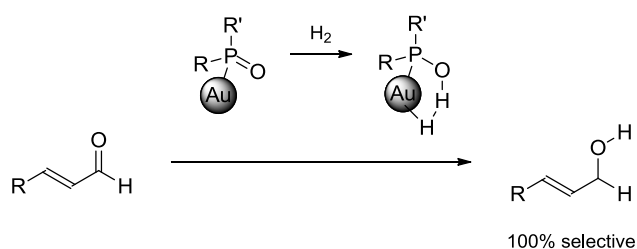
¹⁹⁷ Hollatz, C., Schier, A., Schmidbaur, H. *J. Am. Chem. Soc.* **1997**, *119*, 8115-8116; Hollatz, C., Schier, A., Riede, J., Schmidbaur, H. *J. Chem. Soc., Dalton Trans.* **1999**, 111-113; Hollatz, C., Schier, A., Schmidbaur, H. *Inorg. Chim. Acta* **2000**, *300-302*, 191-199.

with Me₂S afforded [Ph₂P(OH)AuCl]₂ in excellent yield, as a dimeric assembly resulting from two OH-Cl hydrogen bonds and an aurophilic interaction (*Scheme 125*).



Scheme 125 Synthesis of [Ph₂P(OH)AuCl]₂ by Ligand Exchange with Me₂S

Van Leeuwen used [tBu(naphthalen-1-yl)P(OH)AuCl]₂ as a precursor for gold nanoparticles that proved to be highly active catalysts for the chemoselective hydrogenation of substituted aldehydes (*Scheme 126*). In this reaction, the authors speculate a crucial role of the SPO ligand in the heterolytic cleavage of hydrogen *via* a metal-ligand cooperative mechanism. It is also worth mentioning that important differences in the polarity of the P-O bond depending on the nature of R and R' substituents were found, resulting in a pronounced ligand effect.¹⁹⁸



Scheme 126 Heterolytic Cleavage of Hydrogen by SPO-Stabilized Gold Nanoparticles

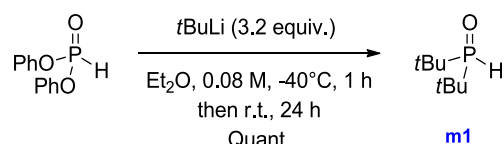
Thus, secondary phosphine oxides bear several advantages, in that they are easy to prepare, stable to oxidation and aqueous media, and the phosphorus center becomes stereogenic when R and R' are distinct, which offers an opportunity for asymmetric catalysis. In this context, our goal was to prepare a series of new SPO-gold(I) complexes and engage both the protonated and deprotonated forms of the ligand in several test reactions such as the cycloisomerization of 1,6-enynes or intermolecular additions, in order to explore their catalytic potential and evaluate their electronic properties.

II. Preparation of SPO-Gold(I) Complexes

¹⁹⁸ Cano, I., Chapman, A.M., Urakawa, A., van Leeuwen, P.W.N.M. *J. Am. Chem. Soc.* **2014**, *136*, 2520-2528; Cano, I., Huertos, M.A., Chapman, A.M., Buntkowsky, G., Gutmann, T., Groszewicz, P.B., van Leeuwen, P.W.N.M. *J. Am. Chem. Soc.* **2015**, *137*, 7718-7727.

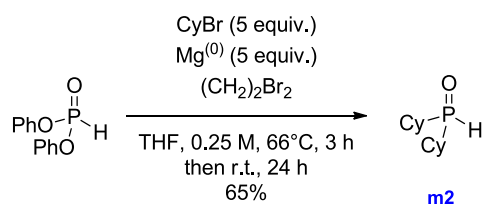
1. Synthesis of SPOs

Five differently substituted SPOs were prepared according to the procedures reported by Buono and Giordano.¹⁹⁹ Depending on the nature of the substituents borne by the phosphorus atom, distinct conditions were used. The di-*tert*butylphosphine oxide **m1** was obtained quantitatively on the mmol scale from two successive nucleophilic additions of *t*BuLi onto the commercially available diphenylphosphite (*Scheme 127*).



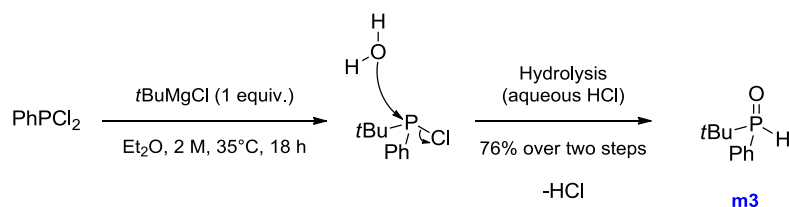
Scheme 127 Synthesis of di-tert-Butylphosphine Oxide m1

Cyclohexylmagnesium bromide was preferentially used as the nucleophile in the synthesis of the dicyclohexylphosphine oxide **m2**, so that the latter was obtained in 65% yield on the 10 mmol-scale (*Scheme 128*).



Scheme 128 Synthesis of Dicyclohexylphosphine Oxide m2

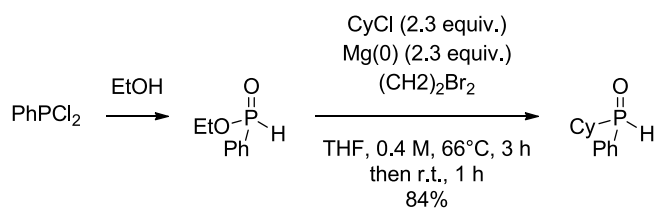
When it comes to the preparation of the (\pm)-*tert*butylphenylphosphine oxide **m3**, dichlorophenylphosphine was used as the starting material to which 1 equivalent of the commercially available *tert*butylmagnesium chloride was added, followed by hydrolysis with aqueous HCl to furnish the expected product in 76% yield on the 10 mmol-scale (*Scheme 129*).



Scheme 129 Synthesis of (\pm)-tert-Butylphenylphosphine Oxide m3

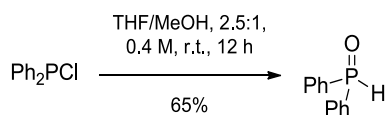
¹⁹⁹ Bigeault, J., Giordano, L., Buono, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4753-4757; Achard, T., Giordano, L., Tenaglia, A., Gimbert, Y., Buono, G. *Organometallics* **2010**, *29*, 3936-3950.

Finally, the (\pm)-cyclohexylphenylphosphine oxide was formed in two steps from the commercially available dichlorophenyl phosphine. The latter was stirred in EtOH to afford ethyl phenylphosphinate before 1 equivalent of cyclohexylmagnesium chloride was added. The desired product was obtained in 84% yield on the 10 mmol-scale (*Scheme 130*).



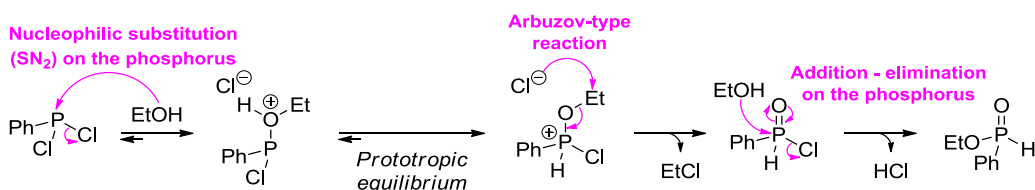
Scheme 130 Synthesis of (\pm)-Cyclohexylphenylphosphine Oxide

The diphenylphosphine oxide is commercially available. Alternatively, it was readily prepared from chlorodiphenyl phosphine in 65% yield on the mmol-scale (*Scheme 131*).



Scheme 131 Synthesis of Diphenylphosphine Oxide

From a mechanistic point of view, the formation of both cyclohexylphenyl- and diphenylphosphine oxides relies on an Arbuzov-type reaction. As a representative example, the proposed mechanism for the formation of ethyl phenylphosphinate from dichlorophenylphosphine is represented below (*Scheme 132*).

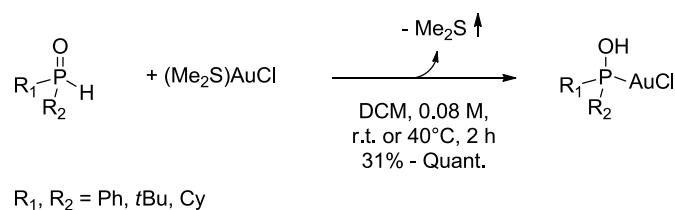


Scheme 132 Proposed Mechanism of the Formation of Ethyl Phenylphosphinate from Dichlorophenylphosphine

2. Coordination of SPO Ligands to Gold(I)

The prepared SPO ligands were then reacted with (dimethyl sulfide)gold(I) chloride in dichloromethane and, after partial evaporation of dichloromethane, the corresponding gold(I) complexes **m4-m7** were isolated by precipitation from pentane, according to Schmidbauer's

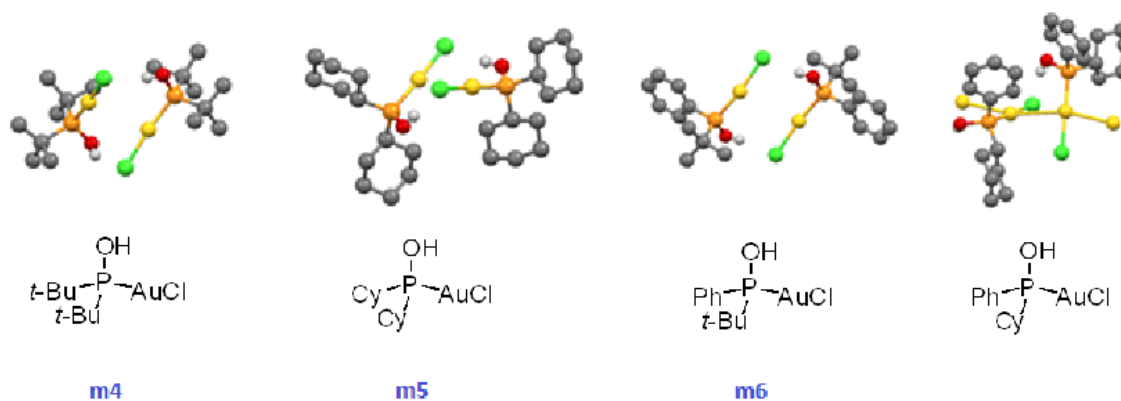
procedure (Table 34).²⁰⁰ The clear dependency of the isolated yield on the nature of the R substituents is worth mentioning. The more electron-donating are the substituents borne by the phosphorus atom, the more coordinating is the ligand. Hence, the formation of the corresponding gold(I) complexes should be easier in the case of strongly electron donating substituents on the phosphorus. However, cyclohexyl and *tert*butyl groups are not only strongly electron-donating but also more sterically demanding than the phenyl group, so that in those two cases, the ligand exchange between Me₂S and the SPO is not favoured, all the more than the boiling point of dimethyl sulfide is situated between 35 and 40°C, which means that it at least partially remains in the reaction mixture at room temperature and is able to coordinate to gold chloride again, thus rendering the reaction reversible. Heating the reaction to reflux aided the conversion to some extent, though the isolated yields of dicyclohexyl- and di-*tert*butylphosphine oxide-gold(I) complexes were low, owing to the fact that the desired SPO-gold(I) complexes are difficult to isolate from the reaction mixture in the case of incomplete reactions. Moreover, it was noticed that the quality of the solvents used for the precipitation step has a drastic impact on the ease of precipitation.



Entry	R ₁	R ₂	Temperature	Product	Yield
1	<i>t</i> Bu	<i>t</i> Bu	40°C	m4	31%
2	Cy	Cy	40°C	m5	44%
3	Cy	Ph	r.t.	-	64%
4	<i>t</i> -Bu	Ph	r.t.	m6	88%
5	Ph	Ph	r.t.	m7	Quant.

Table 33 Synthesis of Various SPO - Gold(I) Complexes

²⁰⁰ Hollatz, C., Schier, A., Riede, J., Schmidbaur, H. *J. Chem. Soc., Dalton Trans.* **1999**, 111-113.



Scheme 133 Crystal Structures of New SPO - Gold(I) Complexes

A crystal structure was obtained for each of the five gold complexes (*Scheme 133*). Except for CyPhP(OH)AuCl which is polymeric, all complexes are dimeric and interconnected by two OH-Cl hydrogen bonds and an aurophilic interaction, though to a weaker extent than reported by Schmidbaur, since the Au-Au distances are between 3.35 and 3.75 Å as compared to 3.11 Å in the case of [Ph₂P(OH)AuCl]₂ (*Table 35*).

Entry	Gold Complex		OH(1)...Cl(2) (Å)	OH(2)...Cl(1) (Å)	Au(1)...Au(2) (Å)
1	tBu ₂ P(OH)AuCl	m4	2.374	2.223	3.349
2	Cy ₂ P(OH)AuCl	m5	2.177	2.224	3.390
3	tBuPhP(OH)AuCl	m6	2.207	2.207	3.748
4	Ph ₂ P(OH)AuCl	m7	2.029	2.105	3.111

Table 34 Characteristic Bond Lengths of SPO – Au^(I)Cl

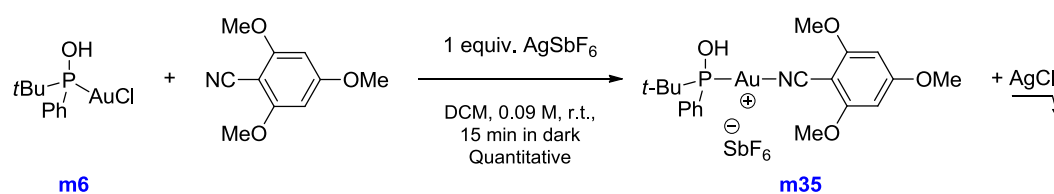
In addition to that, all complexes show bent P-Au-Cl angles (*Table 36*). Similar P-Au-Cl angles deviating from linearity have been found in gold complexes bearing very bulky biarylphosphines.²⁰¹ In our case, we ascribed the values of the P-Au-Cl angles to the dimeric assembly which would generate constraints favouring the nonlinearity.

²⁰¹ Herrero-Gomez, E., Nieto-Oberhuber, C., Lopez, S., Benet-Buchholz, J., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455; Barabé, F., Levesque, P., Korobkov, I., Barriault, L. *Org. Lett.* **2011**, *13*, 5580.

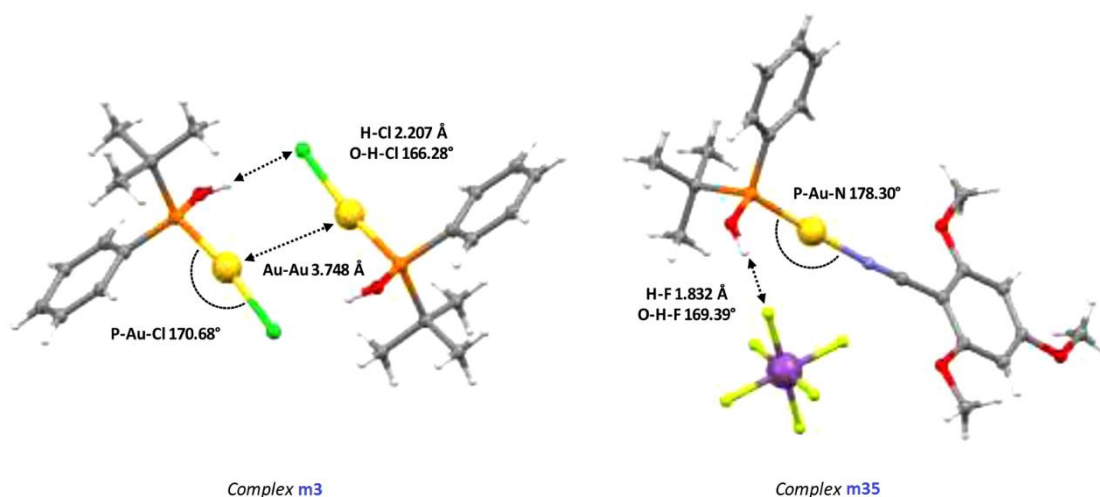
Entry	Gold Complex		$P(1)-Au(1)-Cl(1)$ (deg)	$P(2)-Au(2)-Cl(2)$ (deg)
1	$tBu_2P(OH)AuCl$	m4	175.59(9)	173.3(1)
2	$Cy_2P(OH)AuCl$	m5	174.58	175.15
3	$tBuPhP(OH)AuCl$	m6	170.68	170.68
4	$Ph_2P(OH)AuCl$	m7	169.18	170.85

Table 35 Characteristic Bond Angles of $SPO - Au^{(I)}Cl$

To probe this hypothesis, we prepared the cationic complex by treatment of **m6** with 1 equiv of $AgSbF_6$ in the presence of 1 equiv of 2,4,6-trimethoxybenzonitrile in CH_2Cl_2 (Scheme 134). A quantitative yield was obtained, and a single crystal X-ray diffraction analysis revealed a monomeric structure featuring a $P-Au-N$ angle of 178.30° (Scheme 135). This confirmed our assumption that the dimeric arrangement was responsible for the angle deviation.



Scheme 134 Synthesis of a Stable Cationic Gold(I) Complex **m35**

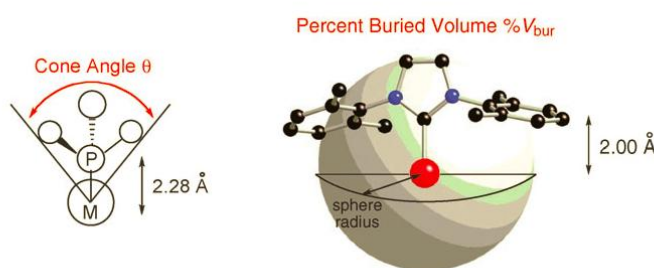


Scheme 135 X-ray Structures of Complexes **m3** (Left) and **m35** (Right)

Tolman proposed to measure the size of a ligand by the cone angle θ defined with the metal at the vertex and the atoms at the perimeter of the cone,²⁰² which parameter is commonly used to classify tertiary phosphine ligands (Scheme 136, left). With more structurally elaborate ligands such as biarylphosphines (Buchwald ligands), bidentate ligands and N-heterocyclic

²⁰² Tolman, C.A. *Chem. Rev.* **1977**, 77, 313-348.

carbenes (NHCs), steric parameter calculations using the Tolman model have proven difficult and sometimes meaningless. Consequently, Nolan and Cavallo proposed another model originally developed to measure the steric bulk of NHC ligands, named “percent buried volume” ($\%V_{\text{bur}}$)²⁰³ and defined as the percent of the total volume of the coordination sphere around a metal occupied by a ligand, *i.e.* the spatial occupation of the ligand (Scheme 136, right). The sphere has a defined radius and the metal center at the core, and the $\%V_{\text{bur}}$ can be calculated using crystallographic data.²⁰⁴ Of note, no metric for SPO ligands has been reported.



Scheme 136 The Tolman Cone Angle (Left) and Percent Buried Volume (Right)

The buried volumes of the prepared SPOs lie in a narrow range (Table 37). Those ligands are less sterically demanding than the corresponding phosphine ligands and it is noteworthy that the more important is the steric hindrance around the phosphorus, the bigger is the gap between the steric demand of the phosphine ligand and that of the corresponding phosphine oxide.

²⁰³ Hillier, A.C., Sommer, W.J., Yong, B.S., Petersen, J.L., Cavallo, L., Nolan, S.P. *Organometallics* **2003**, 22, 4322-4326; Clavier, H., Nolan, S.P. *Chem. Commun.* **2010**, 46, 841-861.

²⁰⁴ The spatial occupation value of the ligands has been obtained using the SambVca (Salerno molecular buried volume calculation) software developed by Cavallo and co-workers that is now available on-line; Poater, A., Cosenza, B., Correa, A., Giudice, S., Ragone, F., Scavaro, V., Cavallo, L. *Eur. J. Inorg. Chem.* **2009**, 1759-1966; <https://www.molnac.unisa.it/OMtools/sambvca.php>. The calculations have been performed by Dr. Hervé Clavier, iSm2.

Entry	Ligand		$d(\text{Au-P})$ (Å)	$V_{\text{bur}}(\%)$ ²⁰⁵
1	$t\text{Bu}_2\text{P}(\text{OH})$	m1	2.232	32.6
2	$\text{P}(t\text{-Bu})_3$		2.252	38.6
3	$\text{Cy}_2\text{P}(\text{OH})$	m2	2.230	28.9
4	PCy_3		2.242	34.1
5	$\text{Ph}_2\text{P}(\text{OH})$		2.220	27.3
6	PPh_3		2.232	30.7
7	$\text{CyPhP}(\text{OH})$		2.238	27.1
8	$t\text{BuPhP}(\text{OH})$	m3	2.225	29.2

Table 36 Au-P Bond Lengths and Percent Buried Volumes (% V_{bur}) of SPO Ligands

III. Preliminary Catalytic Tests

$t\text{BuPhP}(\text{OH})\text{AuCl}$ was selected for preliminary catalytic tests to be conducted, because it had previously been used as a ligand in the literature and because it was intermediate from both an electronic and a steric point of view and thus presumably active in a broader range of reactions. In 2004, Echavarren reported the cycloisomerization of 1,6-enynes catalyzed by phosphine-gold(I) complexes,²⁰⁶ followed by Fürstner²⁰⁷ and Toste.²⁰⁸

1. Mechanistic Considerations

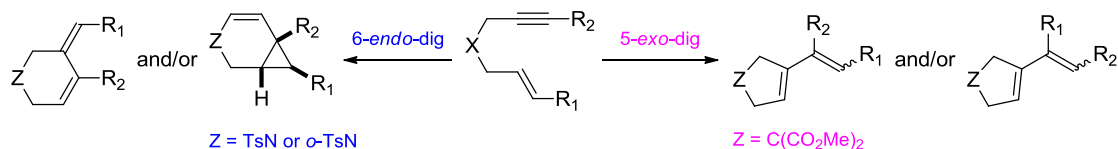
From a mechanistic standpoint, different pathways may be possible depending on the substitution pattern of the substrate. When in the linkage X is TsN or *o*-TsN, formal 6-*endo*-dig cyclization products are mostly obtained (*Scheme 137, left*), whereas 1,6-enynes that include a malonate linkage most often afford 5-*exo*-dig cyclization products. In this latter case, a Thorpe-Ingold effect may be at stake and bring closer both arms of the enyne so that a nucleophilic attack onto the internal position of the alkyne is now favoured (*Scheme 137, right*).

²⁰⁵ The % V_{bur} values have been generated using SambVca with the following settings: 3.5 Å sphere radius; crystallographically determined values for the distance from the center of the sphere; 0.05 Å mesh spacing; hydrogens excluded; bond radii scaled by 1.17.

²⁰⁶ Nieto-Oberhuber, C., Munoz, M.P., Bunnell, E., Nevado, C., Cardenas, D.J., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406. For reviews, see: Zhang, L., Sun, J., Kozmin, S.A. *Adv. Synth. Catal.* **2006**, *348*, 2271; Gorin, D.J., Toste, F.D. *Nature* **2007**, *446*, 395; Jiménez-Núñez, E., Echavarren, A.M. *Chem. Commun.* **2007**, 333; Fürstner, A., Davies, P.W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; Hashmi, A.S.K. *Chem. Rev.* **2007**, *107*, 3211.

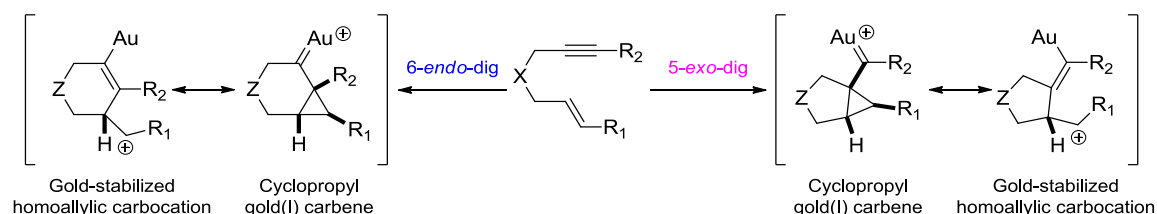
²⁰⁷ Mamane, V., Gress, T., Krause, H., Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654-8655.

²⁰⁸ Luzung, M.R., Markham, J.P., Toste, F.D. *J. Am. Chem. Soc.* **2004**, *126*, 10858-10859.



Scheme 137 6-endo-dig (Left) and 5-exo-dig (Right) Cyclizations

Both the 6-*endo*-dig and the 5-*exo*-dig cyclizations are concerted and stereospecific, and lead to a cyclopropyl gold(I) carbene, which according to DFT calculations is a delocalized cationic, highly distorted structure that is intermediate between a cyclopropyl gold carbene and a gold-stabilized homoallylic carbocation, with low back-donation from gold(I) to the cationic centre (*Scheme 138*).²⁰⁹ The involvement of this intermediate in skeletal rearrangements and other processes has been supported by different trapping experiments.²¹⁰



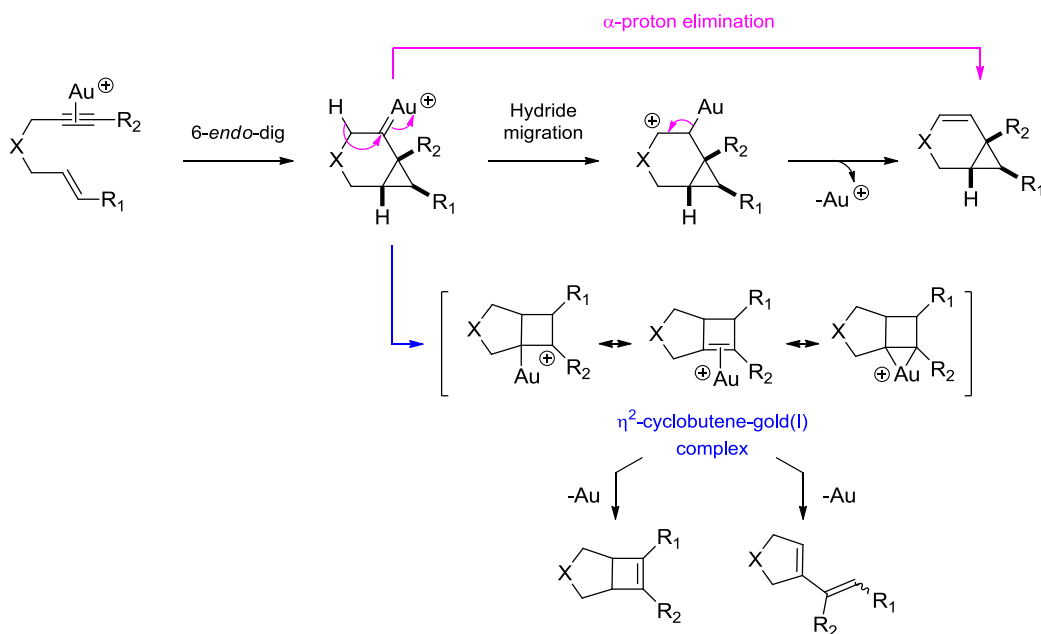
Scheme 138 Concerted Formation of Cyclopropyl Gold(I) Carbenes via 6-endo-dig (Left) and 5-exo-dig (Right) Cyclizations

a) 6-endo-dig Cyclization

The 6-*endo*-dig cyclization is followed by α -proton elimination and affords bicyclic compounds (*Scheme 139*, upper part), or the intermediate of *endo*-dig cyclization can undergo ring expansion to give η^2 -cyclobutene-gold(I) complexes (*Scheme 139*, bottom part) which can evolve to form bicycle[3.2.0]hept-2-ene derivatives (left) or open-up to form dienes in an overall single-cleavage process (right).

²⁰⁹ Nieto-Oberhuber, C., Lopez, S., Munoz, M.P., Cardenas, D.J., Bunuel, E., Nevado, C., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148; Nieto-Oberhuber, C., Munoz, M.P., Lopez, S., Jiménez-Nunez, E., Nevado, C., Herrero-Gomez, E., Raducan, M., Echavarren, A.M. *Chem. Eur. J.* **2006**, *12*, 1677-1693; Escribano-Cuesta, A., Pérez-Galan, P., Herrero-Gomez, E., Sekine, M., Braga, A.A.C., Maseras, F., Echavarren, A.M. *Org. Biomol. Chem.* **2012**, *10*, 6105-6111.

²¹⁰ Amijs, C.H.M., Ferrer, C., Echavarren, A.M. *Chem. Commun.* **2007**, 698-700; Amijs, C.H.M., Lopez-Carrillo, V., Raducan, M., Pérez-Galan, P., Ferrer, C., Echavarren, A.M. *J. Org. Chem.* **2008**, *73*, 7721-7730; Lee, S.I., Chatani, N. *Chem. Commun.* **2009**, 371-384; Lopez, S., Herrero-Gomez, E., Pérez-Galan, P., Nieto-Oberhuber, C., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029-6032; Schlwies, M., Dempwolff, A.L., Rominger, F., Helmchen, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 5598-5601; Schlwies, M., Moser, R., Dempwolff, A.L., Rominger, F., Helmchen, G. *Chem. Eur. J.* **2009**, *15*, 10888-10900.



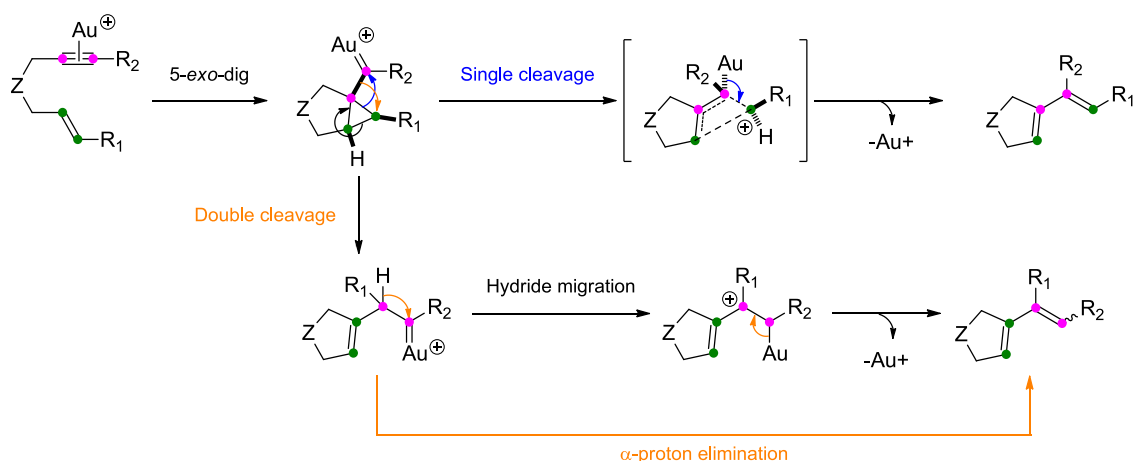
Scheme 139 6-endo-dig Cyclization of 1,6-Enynes

b) 5-exo-dig Cyclization

The intermediate gold carbene resulting from 5-*exo-dig* cyclization is prompt to different types of rearrangements that involve the cleavage of either the alkene alone (single-cleavage skeletal rearrangement) or both the alkene and the alkyne (double-cleavage and endocyclic skeletal rearrangements).

i. Single- and Double-Cleavage Skeletal Rearrangement of 1,6-Enynes

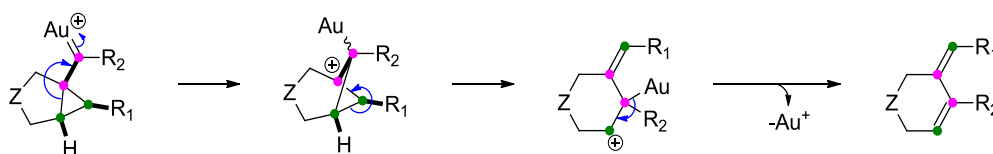
In the single cleavage rearrangement, the alkene configuration of the starting enyne is preserved in a process that involves a 1,3 suprafacial migration of the terminal carbon of the alkene (*Scheme 140*, upper part). Alternatively, the intermediate gold carbene resulting from 5-*exo-dig* cyclization can undergo a double cleavage rearrangement by the formal insertion of the terminal alkene carbon into the alkyne carbons that forms a new gold(I) carbene. The latter then undergo α -proton elimination to give 1,3-dienes. Compounds with *Z* configuration predominate, although both *E* and *Z* configured products have been observed (*Scheme 140*, bottom part).



Scheme 140 Single-cleavage (Upper Part) and Double-cleavage (Bottom Part) Skeletal Rearrangements of 1,6-Enynes

ii. Endocyclic Skeletal Rearrangement of 1,6-Enynes

The product of single *endo* cleavage (Scheme 141) was discovered using cationic gold(I) catalysts and later found in reactions catalysed by InCl_3 , Fe^{III} or Ru^{III} .



Scheme 141 Endocyclic Skeletal Rearrangement of 1,6-Enynes

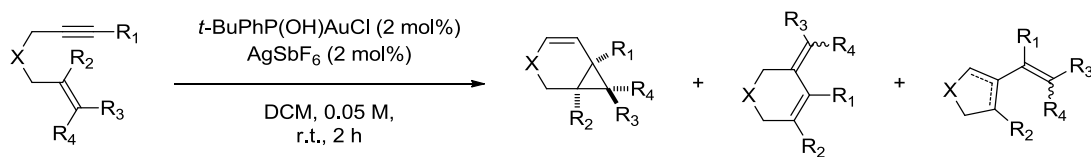
Most 1,6-enynes follow the 5-*exo*-dig cyclization, except for those bearing internal alkynes, which react by the 6-*endo*-dig pathway. This may presumably be correlated to the stabilization of the positive charge initially formed by the coordination of gold to the alkyne.

Several substrates were investigated, that could be classified in three different categories depending on how efficient the reaction was.

2. Efficient Reactions

On condition that the alkene was substituted with an activating group at either its internal or terminal position, the expected products were obtained, from 65% yield when only the alkene is substituted, to 95% yield when a malonate linkage was used and the alkene disubstituted. The more substituted is the terminal position of the alkene, the better (Table 39, entries 4-5). The nature of the linkage, however, has little influence on the efficiency of the

reaction. X can be either *p*- and *o*-tosylamines (Table 38, entries 1-2) or a malonate (Table 38, entries 5-6). Worthy of note, AgSbF₆ alone does not catalyze these reactions²¹¹



Entry	Substrate	Products	Yields	Lit.
1			72%	[Ir] 80% ²¹² [Rh] 58%
2			82%	[Ir] 74% ²¹⁷
3			74%	[Ir] 64% ²¹³
4			65%	[Au] 76% ²¹⁴
5			79%	[Pt] 80% m13 ^{219,215} [Au] 93% m13 [Ag] 21% m13 [Fe] 45% m13
			6%	

²¹¹ Schröder, F., Tugny, C., Salanouve, E., Clavier, H., Giordano, L., Moraleta, D., Gimbert, Y., Mouriès-Mansuy, V., Goddard, J.-P., Fensterbank, L. *Organometallics* **2014**, *33*, 4051.

²¹² Barbazanges, M. Auge, M., Moussa, J., Amouri, H., Aubert, C., Desmarests, C., Fensterbank, L., Gandon, V., Malacria, M., Ollivier, C. *Chem. Eur. J.* **2011**, *17*, 13789-13794; Kim, S.Y., Chung, Y.K. *J.Org.Chem.* **2010**, *75*, 1281-1284.

²¹³ Benedetti, E., Simonneau, A., Hours, A., Amouri, H., Penoni, A., Palmisano, G., Malacria, M., Goddard, J.-P., Fensterbank, L. *Adv. Synth. Catal.* **2011**, *353*, 1908-1912.

²¹⁴ Nieto-Oberhuber, C., Munoz, M.P., Lopez, S., Jiménez-Nunez, E., Nevado, C., Herrero-Gomez, E., Raducan, M., Echavarren, A.M. *Chem. Eur. J.* **2006**, *12*, 1677-1693.

²¹⁵ Fourmy, K., Mallet-Ladeira, S., Dechy-Cabaret, O., Gouygou, M. *Dalton Trans.* 2014, 43, 6728-6734; Nieto-Oberhuber, C., Munoz, M.P., Bunuel, E., Nevado, C., Cardenas, D.J., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406; Koo, J., Park, H.-S., Shin, S. *Tetrahedron Lett.* **2013**, *54*, 834-839.

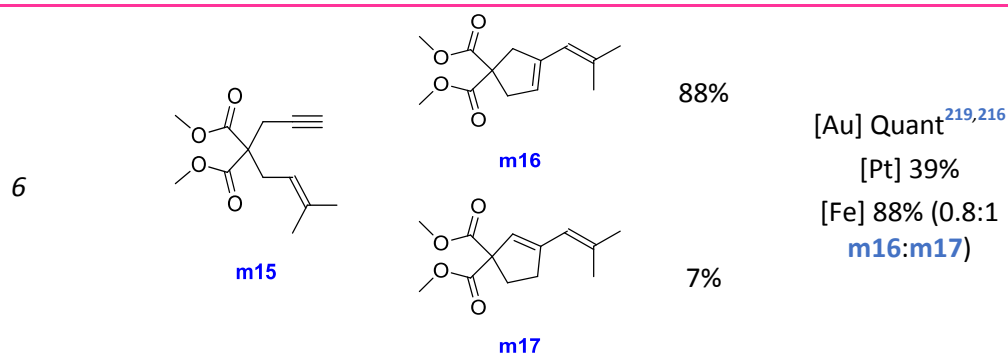
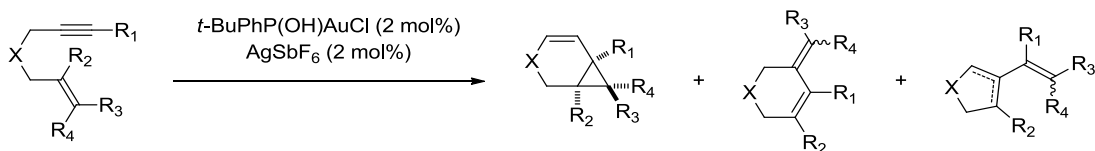


Table 37 Efficient Reactions with *t*BuPhP(OH)AuCl

3. Sluggish Reactions

Especially critical is the substitution of the alkene. A terminal alkyne is indeed tolerated provided that the alkene is not terminal either, as illustrated by the successful cycloisomerization of substrates **m12** and **m15** (65-88% yields; *Table 38*, *Entries 4-6*), whereas the reaction of 1,6-enyne **m18** was sluggish in dichloromethane as well as at reflux of toluene (30 and 31% yield respectively; *Table 39*, *Entries 1-2*). Also sluggish was the reaction when the internal position of the alkene was substituted with a bromine atom. However, a decent yield of the 5-membered ring product was obtained at reflux of toluene (57% yield; *Table 39*, *Entry 4*). Once again, AgSbF₆ alone does not catalyse these reactions.

²¹⁶ Bartolomé, C., Ramiroz, Z., Garcia-Cuadrado, D., Pérez-Galan, P., Raducan, M., Bour, C., Echavarren, A.M., Espinet, P. *Organometallics* **2010**, *29*, 951-956.

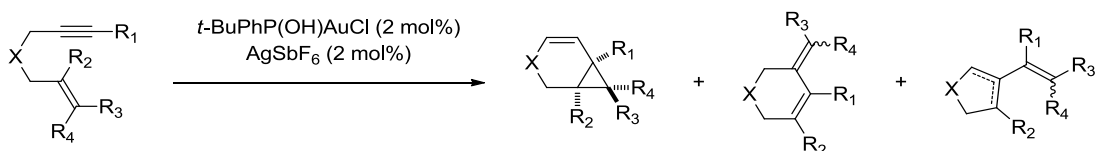


Entry	Substrate	Reaction Conditions	Products	Yields	Lit.
1		DCM, r.t., 2 h		30%	[Ir] 35% ^{218,217}
2	m18	Toluene, 110°C, 24 h	m19	31%	[Rh] 64% [Au] 55% [Pt] 59%
3		DCM, 40°C, 4 h		No reaction	-
4	m20	Toluene, 110°C, 40 h		57%	-

Table 38 Sluggish Reactions with *t*BuPhP(OH)AuCl

4. Non-Working Reactions

Accordingly, no reaction or a very low conversion is obtained when both the alkyne and the alkene are terminal, regardless of the nature of the linkage (TsN or *o*-TsN), even at reflux of dichloromethane for a prolonged reaction time (Table 40).



²¹⁷ Nishimura, T., Maeda, Y., Hayashi, T. *Org. Lett.* **2011**, 13, 3674-3677; Lee, S.I., Kim, S.M., Choi, M.R., Kim, S.Y., Chung, Y.K. *J. Org. Chem.* **2006**, 71, 9366-9372; Fürstner, A., Stelzer, F., Szillat, H. *J. Am. Chem. Soc.* **2001**, 123, 11863-11869; Fürstner, A., Szillat, H., Stelzer, F. *J. Am. Chem. Soc.* **2000**, 122, 6785-6786.

Entry	Substrate	Reaction Conditions	Products	Yields	Lit.
1		DCM, 40°C, 6 h		12%	[Ir] 55% ^{18,222,218} [Pt] 47%
2		DCM, 40°C, 30 h		13%	[Au] 23% [Rh] 66%
3		DCM, 40°C, 8 h		No reaction	-

Table 39 Non-Working Reactions with *t*BuPhP(OH)AuCl

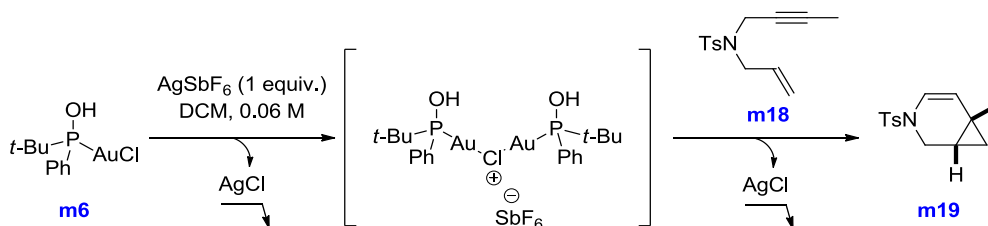
From those results, the following statements can be formulated. *t*BuPhP(OH)AuCl is reactive upon chloride abstraction with a silver salt (AgSbF₆) and can be used in the cycloisomerization of 1,6-enynes. Its efficiency is however substrate-dependent and especially relies on the substitution of the alkene and/or the alkyne, the former being critical for the reaction to perform well. The more substituted is the terminal position of the alkene, the better. Substitution at its internal position was also beneficial except when the substituent was a bromine atom. In this particular case, the reaction was more sluggish. Almost no reaction occurs when both the alkene and the alkyne are terminal. Depending on the nature of the linkage (TsN/*o*-TsN vs. C(CO₂Me)) and the alkyne (terminal or not), different products were obtained, accordingly to what is reported in the literature.

IV. Intervention of a Chloride-Bridged Digold Complex

In order to better understand the results so obtained, the following NMR experiment was performed. Ph₂P(OH)AuCl was dissolved in CD₂Cl₂. ³¹P{¹H} analysis indicated a sharp signal at 89.8 ppm. Upon the addition of 1 equivalent of AgSbF₆, a white precipitate was instantaneously formed, indicative of the precipitation of AgCl and thus of effective chloride abstraction. Novel ³¹P{¹H} analysis showed a broad signal, though the chemical shift was unchanged. Of note, the characteristic signal of the ligand Ph₂P(O)H (δ = 20.7 ppm) was not observed, which means that no decoordination occurred. 1,6-enyne **m18** was then added, and the reaction did proceed within 5 minutes toward the formation of the expected product **m19**. Importantly, the addition of the substrate to the reaction mixture seemed to trigger a new production of AgCl. For this observation to be confirmed, the reaction was repeated with *t*BuPhP(OH)AuCl as the catalyst and the white precipitate of AgCl being filtered off through a Teflon membrane after AgSbF₆ has

²¹⁸ Pradal, A., Chao, C.-M., Toullec, P.Y., Michelet, V. *Beilstein J. Org. Chem.* **2011**, *7*, 1021-1029; Ota, K., Lee, S.I., Tang, J.-M., Takachi, M., Nakai, H., Morimoto, T., Sakurai, H., Kataoka, K., Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 15203-15211.

been added. Accordingly, addition of the substrate to the resulting clear solution led to the formation of a white precipitate (*Scheme 142*).



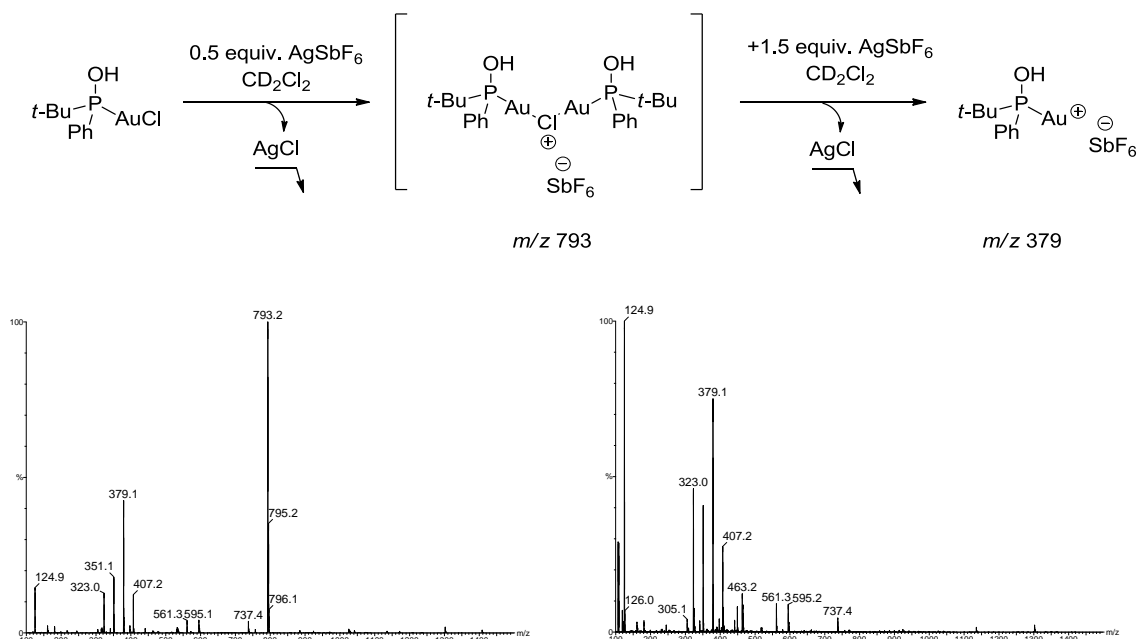
Scheme 142 Precipitation of AgCl by Addition of the Starting Material **m18** to a 1:1 mixture of **m6** and AgSbF_6

This was reminiscent of Echavarren's report on the detrimental formation of chloride-bridged digold complexes.²¹⁹ He indeed showed that abstraction of the chloride anion from Au(I) complexes such as JohnPhosAuCl in non coordinating solvents in the absence of the substrate or if the substrate is not able to effectively cleave the chloride bridge with 1 equivalents of a silver salt, or even larger amounts, leads to the formation of chloride-bridged dinuclear gold(I) complexes, irrespective of the counteranion, which are substantially less reactive as catalysts and that this incomplete removal of the chloride ligand could lead to false negative results when using the *in situ* generation of the gold(I) active species by silver-promoted chloride abstraction.

Such a chloride-bridged complex could not be crystallized nor isolated. Thus, to evidence its existence and in order to determine whether it could be converted into the gold(I) active species in the presence of a larger amount of silver salt, the following $^{31}\text{P}\{^1\text{H}\}$ NMR and mass experiments were performed. 1 equivalent of $[t\text{BuPhP(OH)AuCl}]$ **m6** was mixed in CD_2Cl_2 with 0.25 equiv. of AgSbF_6 . $^{31}\text{P}\{^1\text{H}\}$ NMR showed a broad resonance at 111 ppm, presumably corresponding to $[t\text{BuPhP(OH)AuCl}]$ and other cationic entities, accompanied by a minor and sharper peak at 85 ppm most likely corresponding to a hydrate of the cationic gold(I) complex.²²⁰ The ESI MS spectrum at 60 V revealed a peak at m/z 379 ascribed to the $[t\text{BuPhP(OH)Au}]^+$ fragment and a peak at m/z 793 corresponding to the expected bridged complex $[t\text{BuPhP(OH)AuCl(OH)PtBuPh}]^+$. Charging 0.5 more equivalent of AgSbF_6 gave no observable change in the aspect of the ^1H NMR and mass spectra. However, in the presence of 2 equivalents of AgSbF_6 , while the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum was globally identical, the MS spectrum showed the disappearance of the peak at m/z 379, suggesting strongly that an excess of silver is needed to fully obtain the active cationic complex.

²¹⁹ Homs, A., Escofet, I., Echavarren, A.M. *Org. Lett.* **2013**, *15*, 5782-5785; Bayler, A., Bauer, A., Schmidbaur, H. *Chem. Ber.* **1997**, *130*, 115; Hamel, A., Mitzel, N.W., Schmidbaur, H. *J. Am. Chem. Soc.* **2001**, *123*, 5106; Zhu, Y., Day, C.S., Zhang, L., Hauser, K.J., Jones, A.C. *Chem. Eur. J.* **2013**, *19*, 12264.

²²⁰ Tang, Y., Yu, B. *RSC Adv.* **2012**, *2*, 12686-12689.



Scheme 143 Monitoring of the Formation of a Cationic SPO-Au^I Complex by MS

V. Application to Substrates Responsible for Sluggish Reactions

Those findings were applied to substrates responsible for less efficient reactions, in that 2 equivalents of AgSbF₆ were added relative to the precatalyst when the reaction was sluggish with only 1 equivalent. This proved beneficial, since the expected product **m19** was formed in 61 and 69% yield with *t*BuPhP(OH)AuCl and Ph₂P(OH)AuCl respectively under those conditions (as compared to 30% yield with 1 equivalent of AgSbF₆) (Table 41, entries 1-3). These yields were better than those recorded in the literature, where the best yield was obtained under rhodium catalysis (64%). With PPh₃AuSbF₆, the desired product was formed in 55% yield. The cyclization of **m20** afforded the expected product in 73% yield with *t*BuPhP(OH)AuCl at reflux of toluene (as compared to 57% with 1 equivalent of AgSbF₆ in otherwise the same conditions) (Table 41, entries 4-5). Unfortunately, reactions involving substrates with none of the alkene or the alkyne being substituted did not proceed either with 2 equivalents of AgSbF₆ relative to the precatalyst.

Entry	Substrate	Products	Conditions	Yields
1			<i>t</i> -BuPhP(OH)AuCl (2 mol%) AgSbF ₆ (2 mol%)	30%

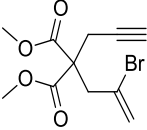
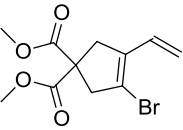
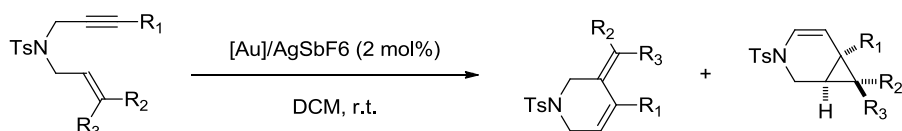
			DCM, r.t., 2 h	
2			<i>t</i> -BuPhP(OH)AuCl (2 mol%) AgSbF ₆ (4 mol%) DCM, r.t., 2 h	61%
3			Ph ₂ P(OH)AuCl (2 mol%) AgSbF ₆ (2 mol%) DCM, r.t., 2 h	69%
4			<i>t</i> -BuPhP(OH)AuCl (2 mol%) AgSbF ₆ (2 mol%) Toluene, 110°C, 40 h	57%
5	m20		<i>t</i> -BuPhP(OH)AuCl (2 mol%) AgSbF ₆ (4 mol%) Toluene, 110°C, 40 h	73%

Table 40 Improvement of Yields in the Presence of 2 Equivalents of AgSbF₆

VI. Ligand Effect

There are many examples of a slight improvement in the reaction yield or efficiency by the right choice of catalyst. Having established the potential of *t*BuPhP(OH)AuCl as a catalyst in the cycloisomerization of 1,6-enynes, we were wondering of a possible ligand effect on the efficiency and/or selectivity in this series of reactions. To probe the possibility of such a ligand effect, some of the substrates were reacted with other SPO-Au(I) catalysts. Whatever the substrate resulted in an efficient or sluggish reaction, absolutely no ligand effect was observed in this series of reactions (Table 41). The same product was isolated with yields in the same range, regardless of the catalyst used. Indeed, a staggering diversity of gold-catalyzed skeletal rearrangements have been discovered for variously substituted and tethered 1,6-enynes, with the product distribution generally being substrate, rather than catalyst dependent. Also, the phosphorous-oxygen bond may be polarized to such an extent that modifications of R groups on the phosphorous are comparatively not significant, thus resulting in the absence of a ligand effect.



Entry	Substrate	[Au]		Product	NMR Yields
2		CyPhP(OH)AuCl			78%
3		<i>t</i> -Bu ₂ P(OH)AuCl	m4		80%
		Cy ₂ P(OH)AuCl	m5		76%
4		m12	<i>t</i> -BuPhP(OH)AuCl		m6
5		CyPhP(OH)AuCl			34%
6		<i>t</i> -Bu ₂ P(OH)AuCl	m4		33%
7		Cy ₂ P(OH)AuCl	m5		34%
8		m18	<i>t</i> -BuPhP(OH)AuCl		m6
9		Ph ₂ P(OH)AuCl	m7		35%
10		CyPhP(OH)AuCl			35%
11		<i>t</i> -Bu ₂ P(OH)AuCl	m4		46%
12		Cy ₂ P(OH)AuCl	m5		45%
14	m21	Ph ₂ P(OH)AuCl	m7		40%

Table 41 Ligand Effect on the Cycloisomerization of 1,6-Enynes **m12**, **m18** and **m21**

In Van Leeuwen's work on SPOs as precursors for gold nanoparticles,¹⁹⁸ important differences were found in the catalytic behaviour of the gold nanoparticles depending on the characteristics of the P-substituents. This was rationalized by the authors as the following:

- the nature of the ligand is determining the size and morphology of the gold nanoparticles.

- nanoparticles prepared with arylsubstituted SPOs present a strong polarity of the P=O bond, whereas those prepared with aliphatic SPOs exhibit a lower polarity of the P=O bond or the presence of POH bonds instead. Since, the P=O bond is involved in the heterolytic cleavage of dihydrogen, nanoparticles prepared with arylsubstituted SPOs show high catalytic activity whereas the heterolytic cleavage is slower when aliphatic SPOs are used.

VII. Other Types of Reaction

The catalytic potential of SPO-Au(I) complexes was further investigated in other types of reactions.

1. Propargyl Ester Migrations

The metal-catalyzed migration of propargyl esters has been extensively investigated.²²¹ The very first report of the 1,2 rearrangement of a propargyl acetate was made by Ohloff in 1976. Using a stoichiometric amount of ZnCl₂ as the Lewis acid, he isolated a mixture of compounds coming from the rearrangement of the propargyl acetate.²²² Another seminal work was made by Rautenstrauch in 1984 under palladium catalysis.²²³ Later, Fensterbank, Malacria and Marco-Contelles showed that PtCl₂ was a very efficient catalyst for such a transformation.²²⁴ The first gold-catalyzed example was published in 2003 by Ohe and Uemura. They reported that metallocarbenoids generated from the [2,3]-rearrangement of propargyl esters undergo intermolecular cyclopropanation with olefins. Ruthenium complexes were optimal catalysts, though AuCl₃ was also examined. They obtained the expected cyclopropanation product, along with 21% of the allenyl acetate coming from the competitive 1,3 rearrangement.²²⁵ The intermolecular cyclopropanation of styrene has been studied by Toste²²⁶ and others,²²⁷ mostly in its enantioselective version. More specifically, Toste noticed ligand effects on the transformation. A stereochemical model accounting for the observed diastereoselectivity was proposed. The cyclopropanation occurs *via* the less sterically encumbered Au carbenoid. The transition state *cis* is favoured over *trans* due to steric clash between the ligand on gold and the substituent on the incoming olefin (*Scheme 145*).²²⁸

²²¹ For reviews on the metal-catalyzed migration of propargyl esters, see: Shu, X.-Z., Shu, D., Schienebeck, C.M., Tang, W. *Chem. Soc. Rev.* **2012**, *41*, 7698-7711; Shiroodi, R.K., Gevorgyan, V. *Chem. Soc. Rev.* **2013**, *42*, 4991-5001; Fensterbank, L., Goddard, J.-P., Malacria, M., Simonneau, A. "Gold-Catalyzed Reaction of Propargylic Esters" in *Homogeneous Gold Catalysis 2014*, Imperial College Press London, 331-391.

²²² Strickler, H., Davis, J.B., Ohloff, G. *Helv. Chim. Acta* **1976**, *59*, 1328-1332.

²²³ Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950-952.

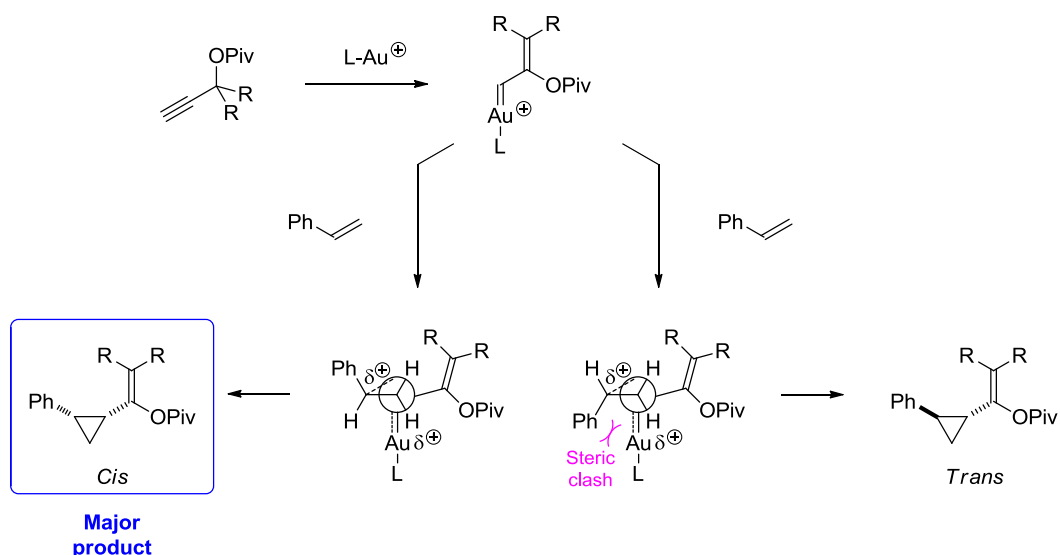
²²⁴ Mainetti, E., Mouriès, V., Fensterbank, L., Malacria, M., Marco-Contelles, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 2132-2135; Marco-Contelles, J., Arroyo, N., Anjum, S., Mainetti, E., Marion, N., Cariou, K., Lemièrre, G., Mouriès, V., Fensterbank, L., Malacria, M. *Eur. J. Org. Chem.* **2006**, 4618-4633.

²²⁵ Miki, K., Ohe, K., Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505-8513.

²²⁶ Johansson, M.J., Gorin, D.J., Staben, S.T., Toste, F.D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003; Gross, E., Liu, J.H.-C., Toste, F.D., Somorjai, G.A. *Nature Chem.* **2012**, *4*, 947-952; Gross, E., Li, J.H., Alayoglu, S., Marcus, M.A., Fabra, S.C., Toste, F.D., Somorjai, G.A. *J. Am. Chem. Soc.* **2013**, *135*, 3881-3886.

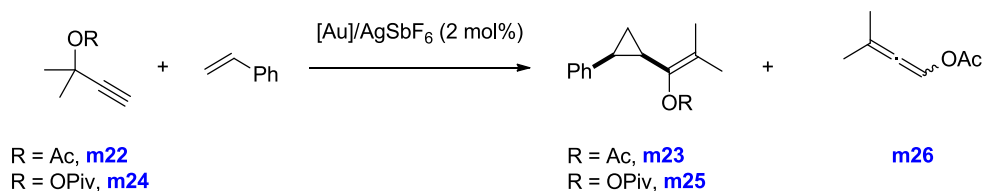
²²⁷ Miki, K., Ohe, K., Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505-8513; Miki, K., Ohe, K., Uemura, S. *Tetrahedron Lett.* **2003**, *44*, 2019-2022; Bartolomé, C., Garcia-Cuadrado, D., Ramiro, Z., Espinet, P. *Inorg. Chem.* **2010**, *49*, 9758-9764.

²²⁸ Johansson, M.J., Staben, S.T., Toste, F.D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.



Scheme 144 Stereochemical Model Accounting for the Cis Stereoselectivity in the Gold-Catalyzed Intermolecular Cyclopropanation of Styrene

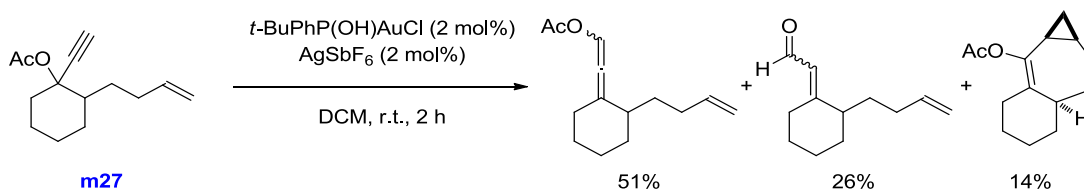
The reaction was first explored in the presence of propargyl acetate **m22**. Unfortunately, very low yields (8-10%) of the expected product were obtained with either $t\text{Bu}_2\text{P}(\text{OH})\text{AuCl}$ or $\text{Ph}_2\text{P}(\text{OH})\text{AuCl}$ when 1 equivalent of styrene was used (*Table 42, entries 1-2*). The efficiency of the reaction could be improved to some extent by increasing the amount of styrene in the reaction mixture but the yields remained below 30% (*Table 42, entries 3-4*). Along with the cyclopropanation product, traces of allenyl acetate **m26** were also observed. The low yields of **m23** may be explained by the preferential 1,3-migration of the propargyl acetate to form **m26**, which is difficult to isolate because of its volatility. Worthy of note, the reaction was totally diastereoselective since only the *cis*-diastereomer was formed, though according to their percent buried volumes, SPO ligands are not very sterically demanding. Even with propargyl pivalate **m24** as the substrate and MeNO_2 as the solvent, accordingly to the best conditions reported by Toste, the desired product was still obtained in similar yields (34%) (*Table 42, entry 5*). The *trans* diastereomer was also isolated in this case (3%). As in the cycloisomerization of 1,6-enynes, no ligand effect was observed in this series of reactions.



Entry	R	Neq. X	[Au]	Conditions	NMR Yields		cis:trans	Lit.
					m23/m25	m26		
1	Ac	1	<i>t</i> Bu ₂ P(OH)AuCl	DCM, r.t., 1 h	10%	-	1:0	
2	Ac	1	Ph ₂ P(OH)AuCl	DCM, r.t., 1 h	8%	-	1:0	[Au]
3	Ac	5	Cy ₂ P(OH)AuCl	DCM, r.t., 1 h	27%	-	1:0	70%
4	Ac	5	Ph ₂ P(OH)AuCl	DCM, r.t., 1 h	31%	-	1:0	>20:1
5 ²²⁹	Piv	5	Ph ₂ P(OH)AuCl	MeNO ₂ , r.t., 24 h	37%	32%	10:1	<i>cis:trans</i>

Table 42 Ligand Effect on Propargyl Ester Migration

Regarding the intramolecular cyclopropanation of propargyl acetate **m27**, a complex mixture was obtained, among which the cyclopropanation product was isolated in low yields. The reaction was more favourable to the formation of the allenyl acetate (51%). A significant amount of its hydrolysis product was also isolated (26%) (Scheme 147). Comparatively, the cyclopropanation product was obtained in 98% yield with PtCl₂ and 61% yield with PPh₃AuSbF₆, along with 32% of the allenyl acetate.²³⁰



Scheme 145 Intramolecular Cyclopropanation of Propargyl Acetate **m27**

Overall, it seems that SPO-gold(I) complexes are not efficient catalysts for 1,2-migration of propargyl esters and subsequent cyclopropanation. The 1,3-migration seems to be favoured over the 1,2-migration pathway.

²²⁹ Isolated yields

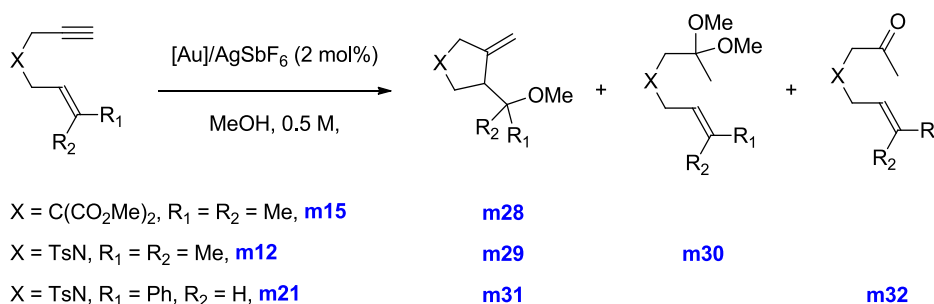
²³⁰ Moreau, X., Goddard, J.-P., Bernard, M., Lemièrre, G., Lopez-Romero, J.M., Mainetti, E., Marion, N., Mouriès, V., Thorimbert, S., Fensterbank, L., Malacria, M. *Adv. Synth. Catal.* **2008**, *350*, 43-48; Marion, N., Lemièrre, G., Correa, A., Costabile, C., Ramon, R.S., Moreau, X., de Frémont, P., Dahmane, R., Hours, A., Lesage, D., Tabet, J.-C., Goddard, J.-P., Gandon, V., Cavallo, L., Fensterbank, L., Malacria, M., Nolan, S.P. *Chem. Eur. J.* **2009**, *15*, 3243-3260; Moreau, X., Hours, A., Fensterbank, L., Goddard, J.-P., Malacria, M., Thorimbert, S. *Journal of Organometallic Chemistry* **2009**, *694*, 561-565.

2. Nucleophilic Additions

a) Methoxy- and Hydroxycyclizations

Attack of nucleophiles R'OH (alcohols or water) at cyclopropyl gold carbene intermediates gives products of alkoxy- or hydroxycyclization instead of skeletal rearrangement.

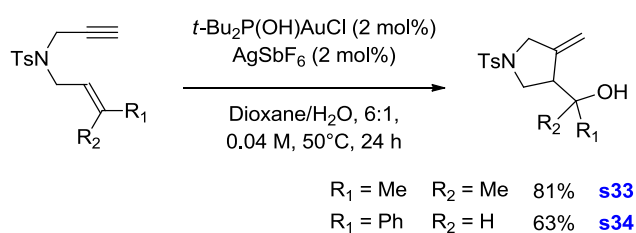
Methoxycyclization products **m28** (89%) and **m29** (81%) were obtained in excellent yields (*Table 43*, entries 1-2). In this latter case, a small amount of compound **m30** resulting from the double addition of methanol onto the alkyne was also isolated (13%) (*Table 43*, entry 2). The reaction was less efficient, however, with enyne **m21** as the starting material. A higher temperature was required in this case, and almost equal quantities of the methoxycyclization and alkyne hydration products were indeed isolated in this case (*Table 43*, entries 3-4).



Entry	X	R ₁	R ₂	[Au]	Temperature and time	Yields		
						m28-m31	m30	m32
1	C(CO ₂ Me) ₂	Me	Me	<i>t</i> Bu ₂ P(OH)AuCl	r.t., 20 h	89%		
2	TsN	Me	Me	<i>t</i> Bu ₂ P(OH)AuCl	r.t., 20 h	81%	13%	
3	TsN	Ph	H	<i>t</i> Bu ₂ P(OH)AuCl	50°C, 3 h	35%		28%
4	TsN	Ph	H	<i>t</i> BuPhP(OH)AuCl	50°C, 3 h	37%		24%

Table 43 Methoxycyclizations

In addition, compounds **m12** and **m21** were successfully engaged in the corresponding hydroxycyclizations (*Scheme 149*, 63 and 81% isolated yield, respectively).



Scheme 146 Hydroxycyclizations

b) Addition of Carbon Nucleophiles

Intermolecular trapping studies were carried out on 1,6-enynes with indoles as nucleophiles, with the highest selectivities for trapping rather than skeletal rearrangement obtained with bulky ligands. However, rather than observing ligand-dependent competition between the nucleophilic addition and skeletally rearranged products, Echavarren instead saw the competitive formation of regioisomeric trapping products (Table 44). Thus, gold(I)-catalyzed additions of carbene nucleophiles to 1,6-enynes give two different types of products by reaction at the cyclopropane or at the carbene carbons of the intermediate cyclopropyl gold carbenes.²³¹ The cyclopropane vs. carbene site selectivity can be controlled in some cases by the ligand on the gold catalyst.²³² When **m21** was used as the starting material, regioisomeric products arising from trapping of the proposed metalcarbenoid were observed. Phosphine and phosphite-based catalysts reacted at the cyclopropane in analogy to a 1,4 addition (Table 44, entries 1-2), while the IMes ligand demonstrated increased selectivity for reaction at the carbene carbon, in analogy to a 1,2 addition (Table 44, entry 3).

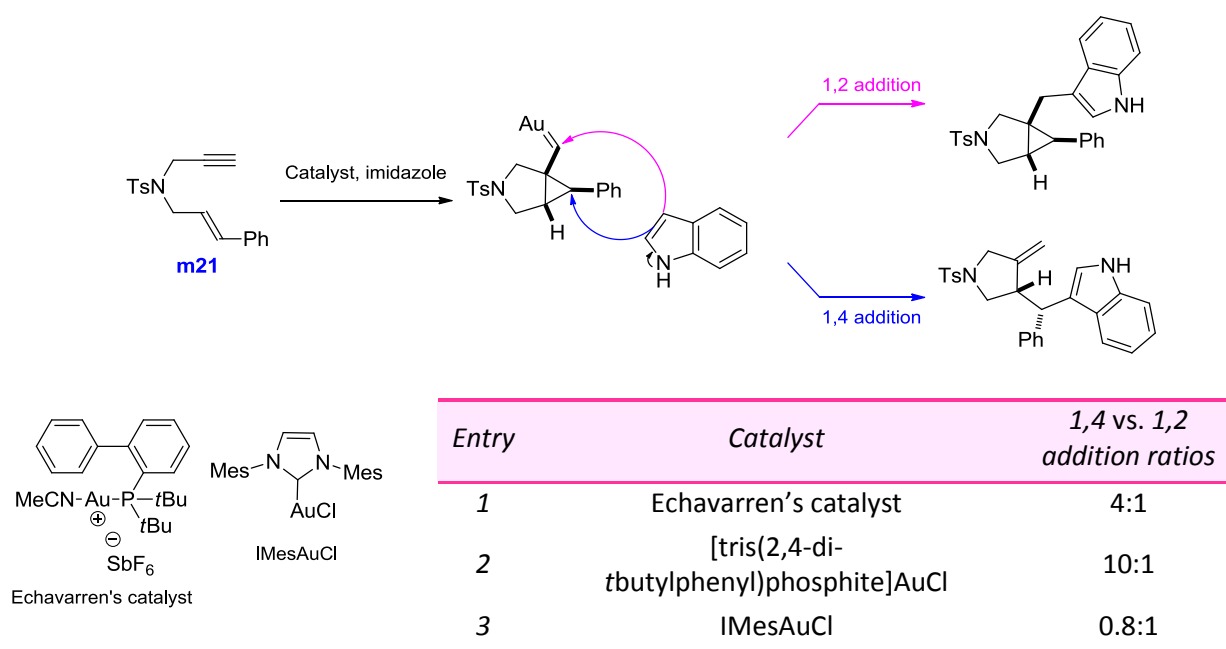
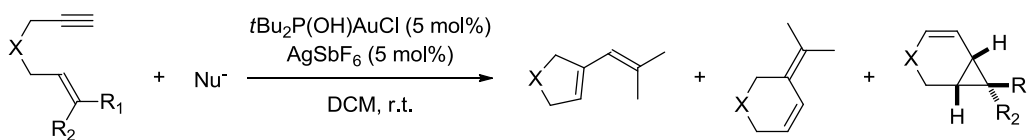


Table 44 Cyclopropane vs. Carbene Site Selectivity as a Function of the Ligand in the Gold(I)-Catalyzed Addition of Indole

Yet, the addition of carbon nucleophiles remained totally unsuccessful. The cycloisomerization products were obtained instead of the expected adducts (Table 45).

²³¹ Amijs, C.H.M., Ferrer, C., Echavarren, A.M. *Chem. Commun.* **2007**, 7, 698-700; Amijs, C.H.M., Lopez-Carrillo, V., Raducan, M., Pérez-Galan, P., Ferrer, C., Echavarren, A.M. *J. Org. Chem.* **2008**, 73, 7721-7730.

²³² De Frémont, P., Clavier, H., Rosa, V., Aviles, T., Braunstein, P. *Organometallics* **2011**, 30, 2241-2251.



Entry	Substrat	Carbon Nucleophile	Products	Yields
1			 m16	54%
			 m35	4%
2			 m13	48%
3			 m21	12%
			 m21	8%
4			 m21	30%
			 m21	3%

Table 45 Attempts Toward the Addition of Carbon Nucleophiles to 1,6-enynes

VIII. Synthesis of a Stable Cationic Gold Complex

The catalytic system employed in the above-mentioned transformations, namely the combined use of a phosphine oxide gold(I) chloride complex and AgSbF_6 as a cocatalyst suffers from the following limitations. AgSbF_6 is very hygroscopic which, in addition to cause difficulties in properly weighting the reagent, may render the reaction medium acidic. Moreover, the active gold(I) species is quite unstable, especially with a fluorine-based counteranion being used, and is

therefore not isolable. Finally, the silver salt may compete the gold(I) complex as a catalyst in some cases.²³³ The “silver effect” on gold(I) catalysis has been discussed by Shi and co-workers.²³⁴ In particular, gold-catalyzed processes were classified into three subgroups on the basis of the role of the silver salt, namely: (i) “genuine” gold catalysis, in which the silver salt exclusively makes cationic the gold halide precursor and does not participate in the reactive event; (ii) gold/silver bimetallic catalysis, in which both metal species are required for the efficiency of the chemical reaction and neither the gold nor the silver alone can promote the reaction; (iii) Ag-assisted Au catalysis; this is probably the most important and popular activation mode in gold catalysis. Here, both metal species are able to promote singularly the chemical process. However, when simultaneously present in solution, they work synergistically, providing better results.

Gagosz described the use of the bis(trifluoromethanesulfonyl)imidate moiety as a weakly coordinating counteranion in the synthesis of stable phosphine gold(I) complexes yet active for the catalysis of a wide range of enynes cycloisomerizations.²³⁵

Thus following the procedure reported by Gagosz, treatment of [tBuPhP(OH)AuCl] **m6** with 1 equivalent of AgNTf₂ was attempted (*Scheme 150*, upper part). Some AgCl precipitated instantaneously, and ³¹P{¹H}NMR showed a broad resonance at 111 ppm, suggesting the formation of the cationic gold complex. tBuPhP(OH)AuNTf₂. Unfortunately, the latter decomposed in solution, so that it could eventually not be isolated pure from the reaction medium. A similar outcome was obtained with 2 equivalents of AgNTf₂ being used.

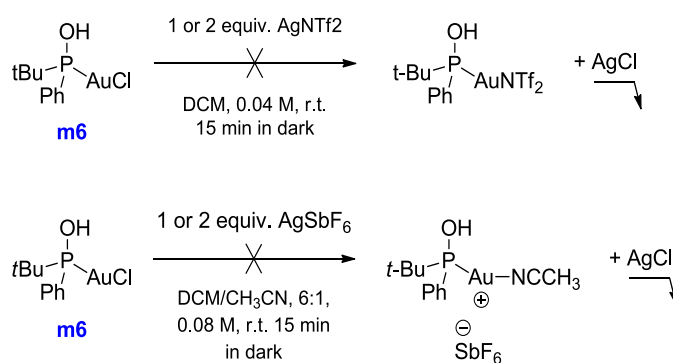
We then turned our attention to the procedure initially reported by Echavarren and later improved by Maier,²³⁶ based on the stabilization of the cationic gold center through its coordination to acetonitrile. Once again, unfortunately, decomposition occurred over time (with 1 or 2 equivalents of AgSbF₆) (*Scheme 150*, bottom part).

²³³ For studies of Ag-mediated reactions, see: Weibel, J.-M., Blanc, A., Pale, P. *Chem. Rev.* **2008**, *108*, 3149-3173; Blanc, A., Tenbrink, K., Weibel, J.-M., Pale, P. *J. Org. Chem.* **2009**, *74*, 5342-5348; Létinois-Halbes, U., Pale, P., Berger, S. *J. Org. Chem.* **2005**, *70*, 9185-9190.

²³⁴ ., Akhmedov, N.G., Zhang, H., Liu, X., Petersen, J.L., Shi, X. *J. Am. Chem. Soc.* 2012, *134*, 9012-9019; Jia, M., Bandini, M. *ACS Catal.* **2015**, *5*, 1638-1652.

²³⁵ Mezailles, N., Ricard, L., Gagosz, F. *Org. Lett.* **2005**, *7*, 4133-4136.

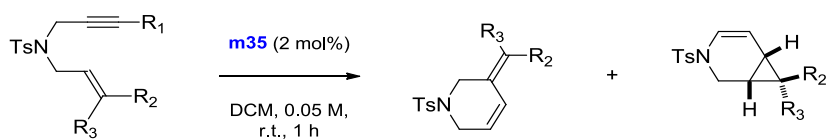
²³⁶ Nieto-Oberhuber, C., Munoz, M.P., Lopez, S., Jiménez-Núñez, E., Nevado, C., Herrero-Gómez, E., Raducan, M., Echavarren, A.M. *Chem. Eur. J.* **2006**, *12*, 1677-1693; Zhdanko, A., Ströbele, M., Maier, M.E. *Chem. Eur. J.* **2012**, *18*, 14732-14744.



Scheme 147 Attempts toward the Synthesis of a Stable Cationic Gold(I) Complex

Therefore, the stable cationic phosphine oxide-gold(I) complex **m35** previously prepared was tested in the cycloisomerization of enyne **m12**. The expected products were obtained in slightly optimized yields as compared to the reaction with SPO-gold(I) complexes **m4-m7** (*Table 46, entry 1*). With more demanding substrates, however, the reaction was sluggish. It is likely that ligand exchange does not occur efficiently with less coordinating substrates, due to the strongly electron-donating character of 2,4,6-trimethoxybenzonitrile (*Table 46, entries 3-4*). Neither the addition of AgSbF_6 nor that of amylene²³⁷ to facilitate the ligand exchange did improve the outcome of the reaction.

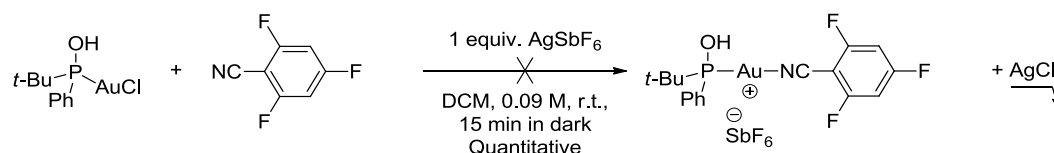
²³⁷ Au(I)-amylene complexes have been detected in some mass experiments.



Entry	Substrate	Products	NMR Yields
1 ²³⁸	 m12	 m13	86%
		 m14	8%
2	 m18	 m19	30%
3	 m21		32%

Table 46 Catalytic Activity of **m35** in the Cycloisomerization of 1,6-enynes

Consequently, the synthesis of a less coordinating yet stable cationic gold complex was attempted by replacing 2,4,6-trimethoxybenzonitrile with 2,4,6-trifluorobenzonitrile, but the resulting complex rapidly decomposed in the reaction medium (*Scheme 151*).



Scheme 148 Attempts toward the Synthesis of a Stable Cationic Gold(I) Complex

We may have some trouble in preparing a stable yet active cationic gold(I) complex because phosphinous acids are not strongly electron donating enough to stabilize the cationic gold(I) centre. Infrared spectroscopy analyses of rhodium- and molybdenum-carbonyl complexes of SPOs have been performed in association to DFT calculations by Buono and co-workers, according to which phosphinous acids should be less donating than the corresponding phosphines. In contrast, phosphinito ligands should be extremely electron-donating.²³⁹ Thus, the

²³⁸ Isolated yields

²³⁹ Martin, D., Moraleda, D., Achard, T., Giordano, L., Buono, G. *Chem. Eur. J.* **2011**, *17*, 12729-12740.

reactivity of phosphinous acids might be compared to that of triphosphite gold complexes while phosphinito ligands should react in the same way as NHCs.

We have attempted to gain further insight into the effects of the protonation state of the phosphinous acid on the availability of the lone pair at the phosphorus from a study of one bond NMR coupling constants between the phosphorus and adjacent acceptor atoms.

The phosphorus couples with the naturally occurring and stable isotope of ^{77}Se (6% natural abundance) and, since 1971 when the first Se-P coupling was reported,²⁴⁰ Se-P couplings have been recorded for hundreds of selenophosphoryl compounds ($\text{Se}=\text{PZ}_3$). The large range of $^1J_{\text{Se-P}}$ values (~ 500 Hz)²⁴¹ provides a sensitive probe of the inductive effect of the phosphorus substituents, since it is well known that coupling constants between directly bonded atoms arise predominantly from the Fermi-contact interaction between nuclear moments and electron spins in s orbitals.²⁴²

The magnitude of $^1J(^{77}\text{Se}-^{31}\text{P})$ is very much dependent upon the nature of the organic groups bound to phosphorus, electron-withdrawing groups causing the coupling constant to increase whereas electron-donating and bulky groups cause it to decrease, these effects being commonly discussed in terms of Bent's rule.²⁴³ The P=Se bond is usually characterized by coupling constants from 500 to 1200 Hz,²⁴⁴ whereas coupling constants between P-Se single bonds range from 300 to 500 Hz.²⁴⁵

Tertiary phosphines react readily with selenium in a refluxing chloroform or toluene solution to form the corresponding phosphine selenide.²⁴⁶ In 2004, Polavarapu and co-workers reported the synthesis and detailed structural study of *tert*butylphenylphosphinoselenoic acid.²⁴⁷ However, no data about the intermediate phosphinito complex was reported. Accordingly, we reproduced the reaction of *tert*butylphenylphosphine oxide with elemental selenium in the

²⁴⁰ McFarlane, W., Nash, J.A. *Chem. Commun.* **1969**, 913; Kroshefsky, R.D., Weiss, R., Verkade, J.G. *Inorganic Chemistry* **1979**, *18*, 469-472.

²⁴¹ Cree, G.M. "The Use of ^{31}P - ^{77}Se Coupling to Characterize the P=Se Bond" **1971**, Perkin-Elmer NMR Quaterly, August, 6; Loginova, E.I., Nuretdinov, I.A., Petrov, Y.A. *Theor. Exp. Chem. (Engl. Transl.)* **1974**, *10*, 47.

²⁴² Pople, J.A., Santry, D.P. *Mol. Phys.* **1964**, *8*, 1; Nixon, J.F., Pidcock, A. *Annu. Rev. NMR Spectrosc.* **1969**, *2*, 345.

²⁴³ Bent, H.A. *Chem. Rev.* **1961**, *61*, 275.

²⁴⁴ Verkade, J.G., Quin, L.D. *Phosphorus – ^{31}P NMR Spectroscopy in Stereochemical Analysis* **1987**, VCM Publishers.

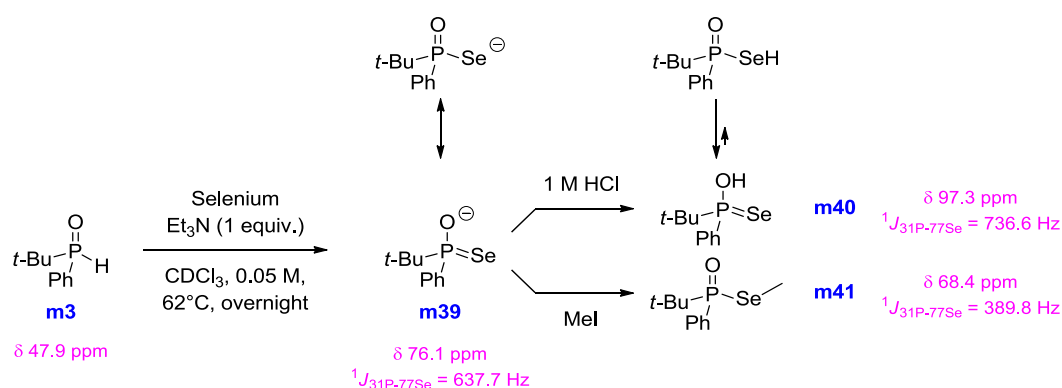
²⁴⁵ Kimura, T., Murai, T. *J. Org. Chem.* **2005**, *70*, 952-959.

²⁴⁶ Allen, D.W., Taylor, B.F. *The Chemistry of Organophosphorus Compounds. Part 15. Phosphorus 31 Nuclear Magnetic Resonance Studies of the Donor Properties of Heteroarylphosphines towards Selenium and Platinum(II)* **1982**, JCS Dalton.

²⁴⁷ Polavarapu, P.L., Wang, F., Dabrowicz, J., Kielbasinski, P., Potrzebowski, M.J., Mikołajczyk, M., Wieczorek, M.W., Majznev, W.W., Lazewska, I. *J. Phys. Chem. A.* **2004**, *108*, 2072-2079.

presence of trimethylamine²⁴⁸ in a refluxing CDCl₃ solution. ³¹P{¹H} NMR analysis of the reaction medium showed a signal at 76.1 ppm and a coupling constant (¹J_{31P-77Se} = 637.7 Hz) consistent with mesomeric structure **m39** and indicative of an extremely electron-donating phosphinito ligand (*Scheme 152*).

Upon hydrolysis with 1 M HCl, *tert*butylphenylphosphinoselenoic acid was obtained (³¹P{¹H} NMR δ 97.3 ppm; sidebands ¹J_{31P-77Se} = 736.6 Hz), in agreement with the data reported by Polavarapu. In a CDCl₃ solution, tautomeric structure **m40** is dominant (*Scheme 152*, upper part). Alternatively, the phosphinito intermediate could be trapped with MeI [³¹P{¹H} NMR 68.4 ppm (sidebands ¹J_{31P-77Se} = 389.8 Hz)], thus confirming its anionic nature (*Scheme 152*, bottom part).



Scheme 149 Study of the Electron-donating Character of tertbutylphenylphosphine Oxide as a Function of its Protonation State

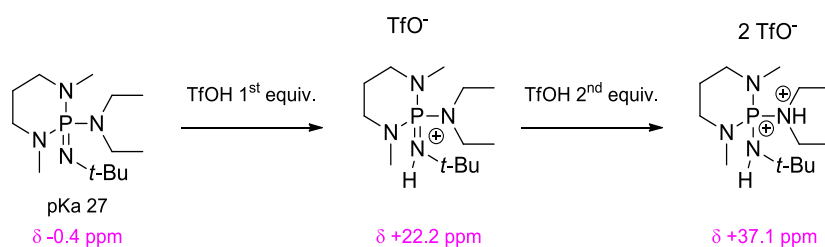
For this reason, the deprotonation of SPO-Au(I) complexes to yield strongly σ -donating phosphinito ligands was considered. Such a deprotonation could in principle occur either before chloride abstraction or on the cationic SPO-gold complex. The acidity of the hydroxyl proton is enhanced in the latter case, though a non-coordinating base would thus be required for the cationic gold centre not to be poisoned. No data relative to the pK_a of SPO-Au(I) complexes has been reported in the literature. The pK_a of SPO-borane complexes, however, has been estimated to be between 4 and 5.²⁴⁹ Accordingly, we believed the pK_a of SPO-Au(I) complexes to approach this value, but neither triethylamine nor the less coordinating DIPEA performed the deprotonation. Nevertheless, the reaction was complete within 30 minutes at room temperature when a phosphazene base was used. Phosphazene bases were developed by Schwesinger *et al.* and are actively studied as strong sterically demanding non-metallic organic

²⁴⁸ Krawiecka, B., Sknzypezynski, Z., Michalski, J. *Phosphorus* **1973**, 3, 177.

²⁴⁹ Stankevici, M., Andrijewski, G., Pietrusiewicz, K.M. *Synlett* **2004**, 2, 311-315.

bases.²⁵⁰ One precious advantage of the phosphazene is that its protonation can be monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR together with the deprotonation of the SPO-gold complex.

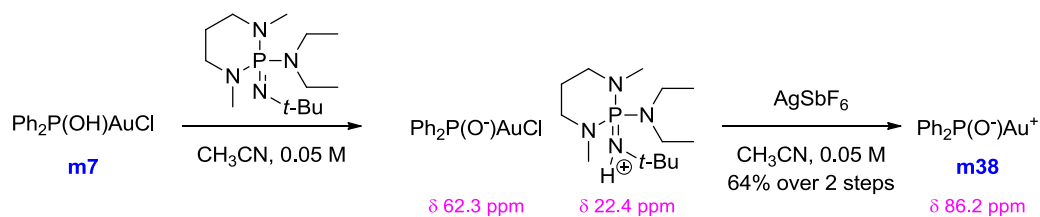
In a preliminary experiment, the phosphazene was reacted in CD_3CN with triflic acid and the reaction monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR to assign its neutral, monoprotinated and bisprotonated forms their characteristic signals (*Scheme 153*). Upon the addition of 1 equivalent of triflic acid, protonation of the phosphazene occurred instantaneously, and the phosphorus atom was strongly deshielded (chemical shift from -0.4 ppm to $+22.2$ ppm). Subsequent addition of a 2nd equivalent of TfOH afforded the bisprotonated species ($\delta +37.1$ ppm). With the characteristic signals of the neutral and monoprotinated species being surely assigned, the phosphazene was used to probe the success or unsuccess of the reaction.



Scheme 150 Neutral, Monoprotinated and Bisprotonated Forms of the Phosphazene Base

$\text{Ph}_2\text{P}(\text{OH})\text{AuCl}$ **m7** was selected as the starting SPO-gold complex to prevent the formation of diastereomers and thus facilitate the monitoring of the reaction. After a 30 minute-stirring at room temperature in the presence of the phosphazene, a black solution was obtained, the $^{31}\text{P}\{^1\text{H}\}$ NMR analysis of which revealed the presence of two signals at 22.4 and 62.3 ppm, ascribed to the monoprotinated phosphazene and deprotonated SPO-gold complex, respectively (*Scheme 154*). Addition of AgSbF_6 to the reaction mixture triggered the instantaneous formation of a white precipitate of AgCl , immediately followed by the precipitation of the desired zwitterionic complex **m38**.

²⁵⁰ Kawai, H., Yuan, Z., Tokumaga, E., Shibata, N. *Org. Biomol. Chem.* **2013**, *11*, 1446-1450; Schwesinger, R., Schlemper, H. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1167; Schwesinger, R., Schlemper, H., Hasenfratz, C., Willaredt, J., Dambacher, T., Breuer, T., Ottaway, C., Fletschinger, M., Boele, J., Fritz, H., Putzas, D., Rotter, H.D., Bordwell, F.G., Satish, A.V., Ji, G.Z., Peters, K., von Schnering, H.G., Walz, L. *Liebigs Ann.* **1996**, 1055.

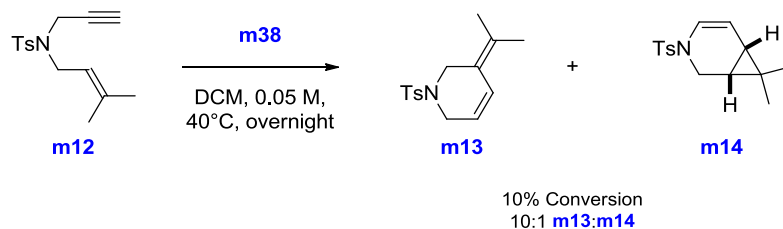


Scheme 151 Formation of Zwitterionic Complex m38

The ion pair formed in the reaction along with **m38** (composed of the protonated phosphazene and hexafluoroantimonate) is soluble in acetonitrile. As none of AgCl or complex **m38** is soluble in this solvent, both of them can be separated from the ion pair by simple filtration of the reaction mixture. Furthermore, while AgSbF₆ is soluble in DCM, **m38** is not. Thus, the pure zwitterionic complex could be isolated by addition of dichloromethane to the crude residue and filtration of the resulting heterogeneous solution. ³¹P{¹H} NMR analysis of the brown powder so obtained showed a sharp signal at 86.2 ppm, consistent with deshielding of the phosphorus atom upon chloride abstraction.

To get further insight into the structure of **m38**, a series of mass experiments were performed. Especially, MALDI-TOF MS analysis of the complex²⁵¹ revealed peaks at *m/z* 797, 1195, 1593 and 1991 ascribed to M₂H⁺, M₃H⁺, M₄H⁺ and M₅H⁺ ions respectively. Accordingly, the ESI MS spectrum²⁵² showed peaks at *m/z* 1593 (M₄H⁺), 1991 (M₅H⁺), 2389 (M₆H⁺) and 2787 (M₇H⁺). Both experiments together suggest that complex **m38** does exhibit an oligomeric structure.

The catalytic potential of **m38** was investigated focusing initially on enyne **m12**, the cycloisomerization of which had been performed in uniformly good yields (76-80%) with all complexes **m4-m7**. In sharp contrast, only a very low conversion of the starting material was observed with the zwitterionic complex, though the products ratio was unchanged (*Scheme 155*).

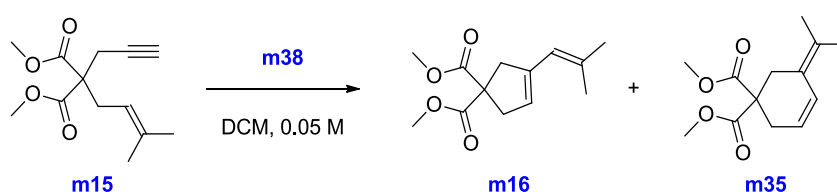


Scheme 152 Reaction of Enyne m12 with Complex m38

²⁵¹ Performed in dichloromethane using a DCTB matrix.

²⁵² Experiment performed at 150 V in CH₃CN. The low mass species are broken at high energy.

Since silver is more oxophilic than gold, we further envisioned the possibility of breaking such an oligomeric structure by adding one equivalent of AgSbF_6 (relative to **m38**) as a cocatalyst. To probe this hypothesis, enyne **m15**, which remains unreacted in the presence of AgSbF_6 alone, was chosen as the starting material. While **m38** was not competent for the cycloisomerization of this substrate, the conversion was complete within 1.5 h at r.t. when the new set of conditions including the addition of AgSbF_6 was used. The 5-*exo*-dig cyclization product was formed in 70% yield, along with a minor amount of the 6-*endo*-dig cyclization product (8% yield) (Table 47).

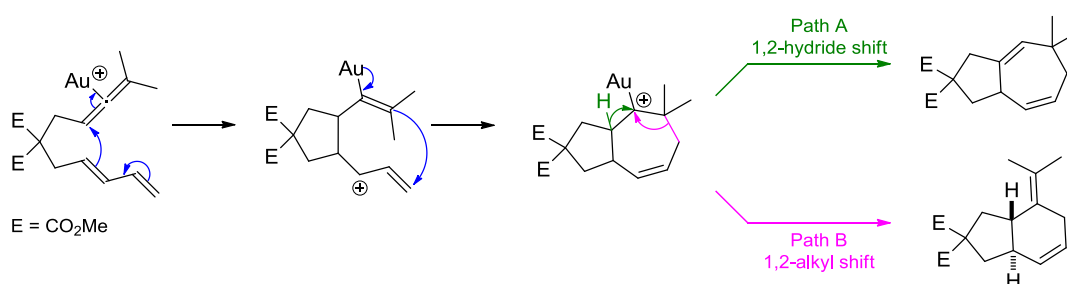
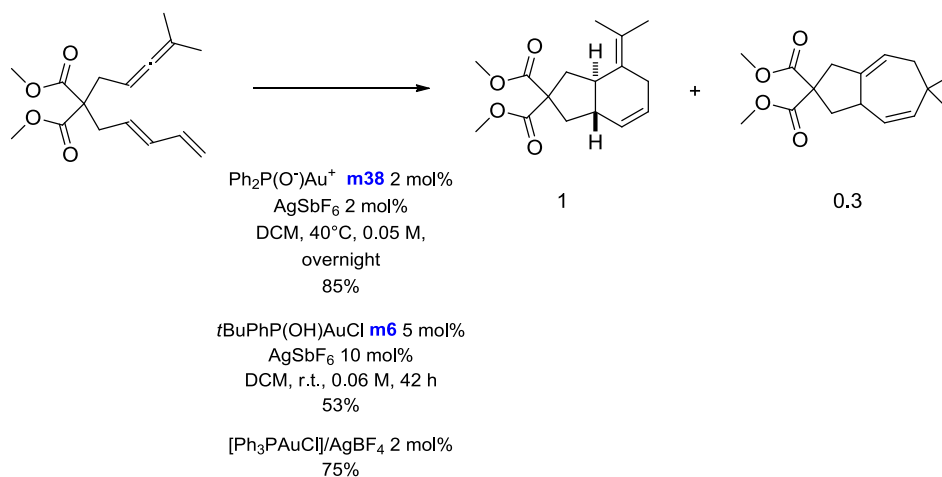


Entry	Nequiv. AgSbF_6	Conditions	Isolated Yields	
1	0	r.t., 20 h	No reaction	
2	1	r.t., 1.5 h	70%	8%

Table 47 Reaction of Enyne **m15** with Complex **m38**

The reaction of allene dienes is known to provide a measure for the donor properties of ligands. π -acidic ligands promote ring contraction by a 1,2-alkyl shift (Scheme 156, Path B) whereas strongly σ -donating ligands favour the 1,2-hydride migration process (Scheme 156, Path A). A 1:0.3 ratio in favour of the ring contraction product was obtained upon the use of **m38** along with an equimolar amount of AgSbF_6 . In comparison, the same ratio was obtained with $t\text{BuPhP}(\text{OH})\text{AuCl}/\text{AgSbF}_6$ or $\text{PPh}_3\text{AuCl}/\text{AgBF}_4$.²⁵³

²⁵³ Petuskova, J., Bruns, H., Alcarazo, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 3799-3802.



Scheme 153 [4+3] vs. [3+2] Cycloadditions in the Presence of **m38**, **m6**/ AgSbF_6 and $[\text{Ph}_3\text{PAuCl}]/\text{AgBF}_4$

This result supports the assumption that phosphinous acids are less donating than the corresponding phosphines. Yet, the absence of an effect of the protonation state of the phosphinous acid on its σ -donating character is surprising. One might argue that the silver ion is too tightly bound to the oxanion for the σ -donating character of the ligand to be affected by the deprotonation.

IX. Conclusions

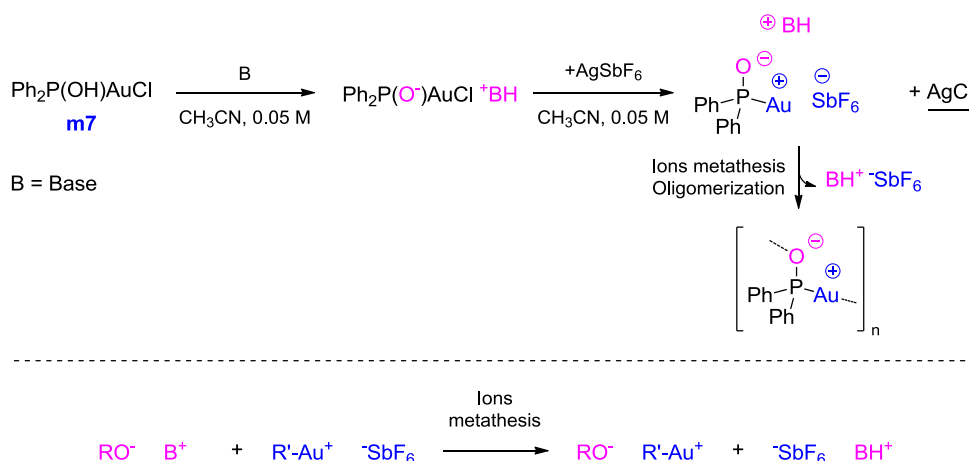
To conclude, secondary phosphine oxides have been successfully prepared and coordinated to gold(I) chloride to afford the corresponding complexes in good yields, the structure of which was determined by X-ray crystallographic analysis. Except for $[\text{CyPhP}(\text{OH})\text{AuCl}]$, which is polymeric, all complexes exhibit a dimeric structure resulting from OH-Cl hydrogen bonds and an aurophilic interaction. In addition, a steric parameter value of SPO ligands has been provided by the calculation of percent buried volumes ($\%V_{\text{bur}}$). Their first use in catalysis has been described and brought confirming elements about the detrimental intervention of chloride-bridged digold complexes previously reported by Echavarren. The nature of the substituents on the phosphinous acid does not seem to have an effect on reactivity or selectivity, maybe because the phosphorous-oxygen bond is polarized to such an extent that

modifications of R groups on the phosphorus are comparatively not significant. Finally, studies are ongoing that aim at investigating the possible modulation of the electronic properties of those ligands upon their deprotonation.

X. Perspectives

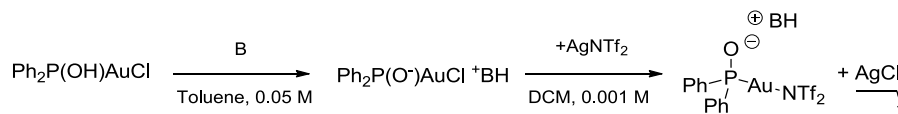
The synthesis of the phosphinito-gold(I) complex may be modified so that a stable, monomeric complex featuring an extremely strong σ -donating and a very weak π -accepting phosphinito ligand be obtained.

Three key parameters may be considered, namely the nature of both the solvent and the silver salt and the concentration of the reaction medium. In the present procedure, acetonitrile has been chosen as a convenient solvent since it cannot be deprotonated by the phosphazene and facilitates the isolation of the complex from the reaction mixture. However, for the phosphinito ligand to exhibit a strongly electron donating character, the oxanion should be naked, which is not possible if the reaction is performed in acetonitrile where it is driven toward the formation of oligomers upon their precipitation. The oligomerization process arises from ions metathesis, such an equilibrium is driven toward the formation of the most thermodynamically stable ion pairs. In other words, it is likely that the soft antimonate anion preferentially associates with the protonated phosphazene rather than with the gold cation, which eventually results in the formation of oligomers. Changing the silver salt featuring a more coordinating counteranion like AgNTf_2 may prevent ions metathesis and thus oligomerization. Also should a diluted reaction medium ($C = 0.001 \text{ M}$) prevent the oligomerization process. Finally, performing chloride abstraction in dichloromethane, where the complex is soluble to some extent, should prevent potentially formed oligomers to precipitate, thus driving the metathesis equilibrium towards the oligomerization process.



Scheme 154 Ions Metathesis in the Synthesis of the Phosphinito-Gold(I) Complex of m7

Since the deprotonation of the phosphinous acid-gold(I) complex cannot be performed in dichloromethane, the synthesis of the desired phosphinito-gold(I) complex would have to be performed in two steps. The deprotonation of the hydroxyl group may be performed in toluene. Then, after evaporation of the solvent would the resulting phosphinito gold(I) chloride complex be dissolved in dichloromethane, where chloride abstraction would be performed.



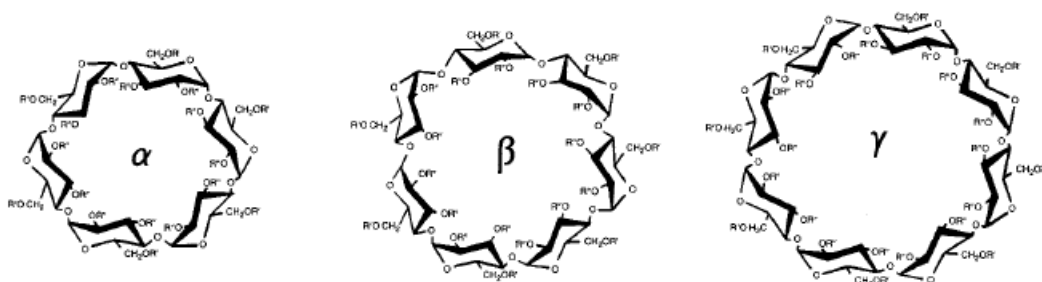
Scheme 155 Strategy Envisioned toward the Synthesis of a Monomeric Phosphinito-Gold(I) Complex of m7

Chapter III

NHC-Capped Cyclodextrin-Gold(I) Complexes

I. Introduction

Cyclodextrins are cyclic oligosaccharides consisting of 6 (α -cyclodextrin), 7 (β -cyclodextrin), 8 (γ -cyclodextrin) or more α -D-glucopyranoside units linked 1- \rightarrow 4 (*Scheme 159*). While they are hydrosoluble compounds, their interior is hydrophobic, so that they have been widely used to host hydrophobic molecules in polar solvents. α -cyclodextrins have small cavities that are not capable of accepting many molecules. In contrast, the cavities of γ -cyclodextrins are much larger than most molecules the incorporation of which is required. Hence, β -cyclodextrins are the most commonly encountered in this field.



Scheme 156 α -, β - and γ -Cyclodextrins

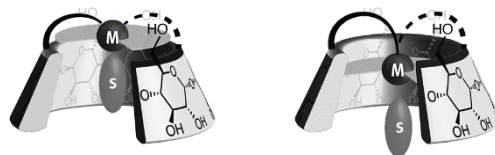
The possibility of converting cyclodextrins into metalloenzymes mimics has soon attracted attention. The attachment of a metal-ligand unit at the entrance of the cavity to mimic the binding pocket of an enzyme in which a substrate can be included has been extensively studied and applied in catalysis.²⁵⁴ However, the metal centre cannot be fixed directly above the cavity through single linkage, so that “metal-capped cyclodextrins”, in which the metal center is attached right on top of the cavity through a double linkage have been developed.²⁵⁵ The deepest position that have been reached so far intercepts the plane defined by the C-6 atoms of the sugar units.²⁵⁶ Thus, the cavity is still available for the inclusion of guests (*Scheme 160*, left).

²⁵⁴ Breslow, R., Overman, L.E. *J. Am. Chem. Soc.* **1970**, *92*, 1075-1077; Reetz, M.T., Waldvogel, S.R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 863-867.

²⁵⁵ Tabushi, I., Kweda, Y. *J. Am. Chem. Soc.* **1984**, *106*, 4580-4584; Armspach, D., Matt, D. *Chem. Commun.* **1999**, 1073-1074; Engeldinger, E., Armspach, D., Matt, D. *Chem. Rev.* **2003**, *103*, 4147-4174.

²⁵⁶ Engeldinger, E., Armspach, D., Matt, D. *Angew. Chem. Int. Ed.* **2001**, *40*, 2526-2529; Poorters, L., Armspach, D., Matt, D., Toupet, L., Choua, S., Turek, P. *Chem. Eur. J.* **2007**, *13*, 9448-9461.

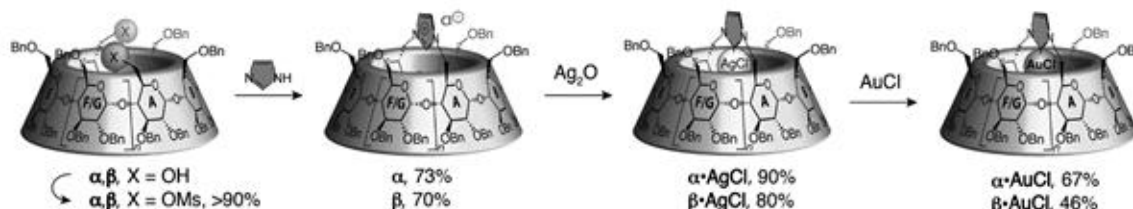
Alternatively, the metal can be encapsulated inside the cavity to mimic the environment of a metal buried deeply within a folded protein cavity. In this latter case, where the metal typically lies at the level of the H-5 atoms, thus occupying the middle of the cavity, only noncovalent inclusion complexes had been described (*Scheme 160*, right).²⁵⁷



Scheme 157 Interaction of Metal-Capped Cyclodextrins with the Substrate (left) or the Metal (right)

Sollogoub and co-workers have yet recently performed the synthesis of NHC-capped cyclodextrins in which the metal atom is embedded in the centre of the cavity.²⁵⁸

α - and β -imidazolium-bridged cyclodextrins are formed in 73 and 70% yield respectively by treatment of the bismesylylated α - and β -cyclodextrins²⁵⁹ with imidazole (*Scheme 161*). The silver-NHC complexes α -AgCl and β -AgCl are then obtained in 90 and 80% yield in the presence of Ag_2O . The gold complex is generated through transmetalation of the silver complex with AuCl to give α -AuCl and β -AuCl in 67 and 46% yield respectively.



Scheme 158 Synthesis of α - and β -ICyDAuCl Catalysts

²⁵⁷ Matsue, T., Evans, D.H., Osa, T., Kobayashi, N. *J. Am. Chem. Soc.* **1985**, *107*, 3411-3417; Cardona, C.M., Mundoza, S., Kaifer, A.E. *Chem. Soc. Rev.* **2000**, *29*, 37-42.

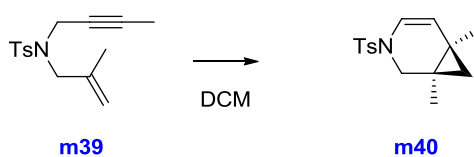
²⁵⁸ (a) For cyclodextrin-based NHCs, see: Legrand, F.-X., Ménand, M., Sollogoub, M., Tilloy, S., Monflrier, E. *New J. Chem.* **2011**, *33*, 2061-2065; Guitet, M., Marcelo, F., de Beaumais, S.A., Zhang, Y., Jiménez-Barbero, J., Tilloy, S., Monflrier, E., Ménand, M., Sollogoub, M. *J. Org. Chem.* **2013**. (b) For cyclodextrin-based phosphines, see: Guieu, S., Zaborova, E., Blériot, Y., Poli, G., Jutand, A., Madec, D., Prestat, G., Sollogoub, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 2314-2318; Zaborova, E., Deschamps, J., Guieu, S., Blériot, Y., Poli, G., Ménand, M., Madec, D., Prestat, G., Sollogoub, M. *Chem. Commun.* **2011**, *47*, 9206-9208.

²⁵⁹ (a) For the synthesis of the perbenzylated diols XX and XX, see: Lecourt, T., Pearce, A.J., Herault, A., Sollogoub, M. *J. Org. Chem.* **2008**, *73*, 2819-2828; Guieu, S., Sollogoub, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7060-7063; Zaborova, E., Blériot, Y., Sollogoub, M. *Tetrahedron Lett.* **2010**, *51*, 1254-1256. (b) For the synthesis of the bismesylylated α - and β -cyclodextrins, see: Deunf, E., Zaborova, E., Guieu, S., Blériot, Y., Verpeaux, J.-N., Buriez, O., Sollogoub, M., Amatore, C. *Eur. J. Inorg. Chem.* **2010**, 4720-4727.

NMR experiments have been performed in conjunction with molecular modelling which indicated a partial inclusion of the imidazolium ring inside the cavity, so that the metal is buried deep and aligned with H-5. In addition, a halogen- π interaction has been evidenced, that is responsible for the benzyl groups to define an intramolecular second coordination sphere, which closes the entrance of the cavity at its wider secondary rim. Interestingly, the cavity entrance can be opened by halide abstraction.

The NHC-capped cyclodextrin ligand displays an exceptionally high $\%V_{bur}$ value (58.5% for a simplified model of the α -cyclodextrin) and the metal is sufficiently insulated to prevent electron transfer, which characteristics raised the question of the accessibility of the metal as a reactive center. Our goal was thus to probe the possibility of catalytic activity and study the effects of the size and chirality of the cavity as compared to NHC-Au complexes.

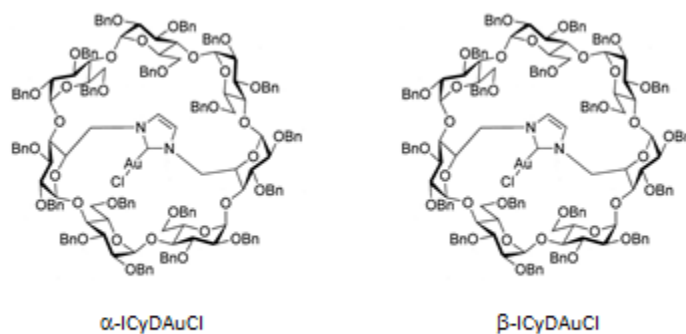
To begin with, a benchmark reaction was studied for which the size of the cavity could be an added value. The 1,6-enyne **m39** (Table 48) had previously been studied by our group and others under rhodium, iridium and platinum catalysis and in all cases, the six-membered-ring product **m40** had been obtained in good yields (61-95%).²⁶⁰ In addition, both rhodium and iridium catalysis allowed very good enantiomeric excesses to be reached (86 and 88% ee respectively). Poor results, however, were obtained under platinum catalysis from an asymmetric induction standpoint (19% ee). Surprisingly had this substrate never been tested under gold catalysis.



Entry	Catalyst	Loading	Temperature	Time	Yields	e.e.
1	α -ICyDAuCl + AgSbF ₆	5 mol%	40°C	15h	83%	43%
2	β -ICyDAuCl + AgSbF ₆	2 mol%	40°C	15h	77%	59%
3	IPrAuCl + AgSbF ₆	2 mol%	r.t.	3h	80%	0%
4	AgSbF ₆	5 mol%	40°C	2 days	No reaction	

Table 48 Cycloisomerization of Enyne **m39** with α - and β -ICyD Catalysts

²⁶⁰(a) For iridium-catalyzed reactions, see: Barbazanges, M. Auge, M., Moussa, J. Amouri, H., Aubert, C., Desmartes, C., Fensterbank, L., Gandon, V., Malacria, M. Ollivier, C. *Chem. Eur. J.* **2011**, *17*, 13789-13794; Benedetti, E., Simmoneau, A., Hours, A., Amouri, H., Penoni, A., Palmisano, G., Malacria, M., Goddard, J.-P., Fensterbank, L. *Adv. Synth. Catal.* **2011**, *353*, 1908-1912; Sim, S.H., Lec., S.I., Park, J.H., Chung, Y.K. *Adv. Synth. Catal.* **2010**, *352*, 317-322. (b) For rhodium-catalyzed reactions, see: Nishimura, T., Maeda, Y., Hayashi, T. *Org. Lett.* **2011**, *13*, 3674-3677; Nishimura, T., Kawamoto, T., Nagaosa, M., Kumamoto, H., Hayashi, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 1638-1641; Kim, S.Y., Chung, Y.K. *J. Org. Chem.* **2010**, *75*, 1281-1284. (c) For platinum-catalyzed reactions, see: Jullien, H. Brissy, D., Sylvain, R., Retailleau, P., Naubron, J.-V., Gladiali, S., Marinetti, A. *Adv. Synth. Catal.* **2011**, *353*, 1109-1124; Fürstner, A., Stelzer, F., Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863-11869; Fürstner, A., Szillat, H., Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785-6786.



Scheme 159 Structures of α - and β -ICyDAuCl Catalysts

The reaction was initially run using α - and β -ICyDAuCl catalysts, along with an equimolar quantity of AgSbF_6 . It is worth mentioning that 21 equivalents of the silver salt are required for the chlorine atom to be fully abstracted from the gold centre in the particular case of in α -ICyDAuCl,²⁶¹ so that a very small quantity of active catalyst is actually contained in the reaction medium when a single equivalent of it is used relative to the catalyst. Full conversion was nevertheless reached with reasonable catalysts loadings of α -ICyDAuCl (5 mol%). IPrAuCl was used as a reference to compare with. Similar yields were obtained with all three catalysts (77–83%, *Table 48, entries 1-3*), although a higher temperature and a much longer reaction time were needed when α - or β -ICyDAuCl was used. No reaction occurred with AgSbF_6 alone (*Table 48, entry 4*). When it comes to stereodifferentiation, better results were obtained with β -ICyDAuCl than with α -ICyDAuCl (59 vs. 43% ee, respectively), whereas the reaction with IPrAuCl as the catalyst logically led to a racemic mixture.²⁶²

Those results can be rationalized by considering the relative sizes of α - and β -ICyD cavities. The cavity of the β -ICyD is not only much larger but also more distorted than that of the α -ICyD. On the one hand, the larger cavity of the β -ICyD would thus give better access to the gold centre, which eventually results in a higher catalyst turnover. On the other hand, the greater distortion of its cavity gives rise to the possibility of asymmetric induction.

From this first series of reactions, it can be concluded that:

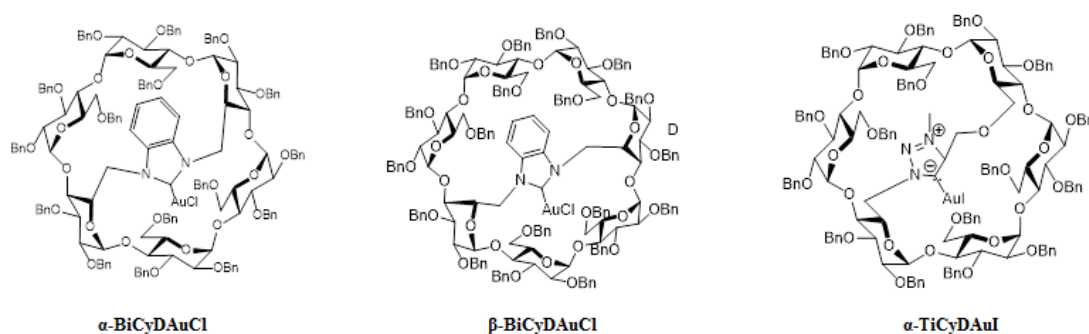
- The encapsulation of gold deep inside the cavities of α - and β -ICyDs does not prevent the metal from being reactive.

²⁶¹ With α -ICyDAuCl was reacted with AgNTf_2 by Sollogoub and co-workers (unpublished result).

²⁶² Guitet, M., Zhang, P., Marcelo, F., Tugny, C., Jiménez-Barbero, J., Buriez, O., Amatore, C., Mouriès-Mansuy, V., Goddard, J.-P., Fensterbank, L., Zhang, Y., Roland, S., Ménand, M., Sollogoub, M. *Angew. Chem. Int. Ed.* **2013**, 52, 7213.

- The size and chirality of both α - and β -ICyD cavities do have an impact on reactivity and enantioselectivity, in that a higher catalyst loading is required with α -ICyDAuCl, the cavity of which is smaller than that of β -ICyDAuCl, and both catalysts made possible a stereodifferentiating process from enyne XX. A better enantiomeric excess was obtained with β -ICyDAuCl, the cavity of which is larger and more distorted than that of α -ICyDAuCl.

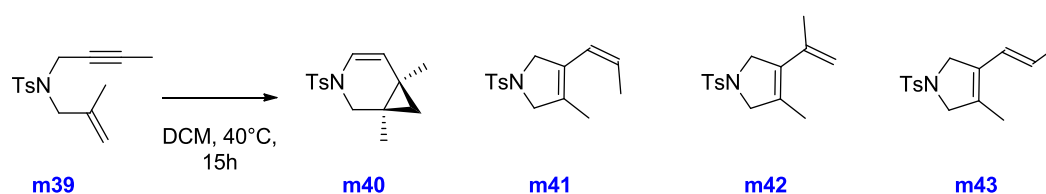
Other NHC-capped cyclodextrin-gold(I) catalysts were prepared by Sollogoub and co-workers and investigated by us in order to determine whether modifications affecting the NHC part of the catalysts would influence the outcome of the reaction and/or the enantiomeric excess. The initial imidazole fragment was thus replaced with a benzimidazole in α - and β -BiCyDAuCl and a mesoionic carbene in α -TiCyDAuI (*Scheme 163*). Especially, the former should be less electron-donating due to the implication of the nitrogens lone pairs into mesomery with the benzene ring while the latter should exhibit a cavity the asymmetry of which is greatly enhanced.



Scheme 160 Structures of α -BiCyDAuCl, β -BiCyDAuCl and α -TiCyDAuI Catalysts

Only 2 mol% of β -BiCyDAuCl allowed the reaction to be complete (*Table 49, entry 2*). In contrast, 5 mol% of catalyst was required when α -BiCyDAuCl and α -TiCyDAuI were used (*Table 49, entries 1 and 3, respectively*). The reactivity of β -BiCyDAuCl was very similar to that of β -ICyDAuCl, with the 6-membered-ring product isolated in 78% yield and 62% *ee* (*Table 49, entry 2*). The enantiomeric excess was slightly improved when the reaction was run at r.t., yet the conversion was not complete. Lower yields and enantiomeric excesses were obtained with α -BiCyDAuCl (63% yield, 26% *ee*) and α -TiCyDAuI (58% yield, 0% *ee*) (*Table 49, entries 1 and 3, respectively*). Particularly surprising was the formation of a racemic mixture when α -TiCyDAuI was used as the catalyst, in spite of the greater asymmetry of its cavity (*Table 49, entry 3*). Side

products were obtained in low yields along with the expected bicyclic compound so that α -ICyDAuCl and β -ICyDAuCl were kept as catalysts of choice. Overall, this second series of reactions confirmed the greater efficiency of the β -cyclodextrin-based catalysts over the α -cyclodextrin-based catalysts.



Entry	Catalyst	Loading	Yields	ee
1	α -BiCyDAuCl + AgSbF ₆	5 mol%	m40: 63%	26%
			m41: 7%	
			m42: 1%	
2	β -BiCyDAuCl + AgSbF ₆	2 mol%	m40: 78%	62% at 40°C
			m41: 6%	68% at r.t.
			m42: 6%	
3	α -TiCyDAuI + AgSbF ₆	5 mol%	m40: 58%	0%
			m41: 2%	
			m42: 2%	
			m39: 11%	

Table 49 Cyclization of Enyne **m39** with other Cyclodextrin-Based Catalysts

Then, the solvent was screened (Table 50). When the reaction was run in dioxane alone as the solvent, the conversion was very low. One might imagine dioxane to get inside the cavity and compete with the substrate. The conversion was complete, however, when a 5:3 mixture of dioxane and dichloromethane was used instead (Table 50, entry 1). Toluene was also investigated (Table 50, entry 2). Nonetheless, no enantiomeric excess was obtained, neither in the dioxane/dichloromethane mixture nor in toluene.



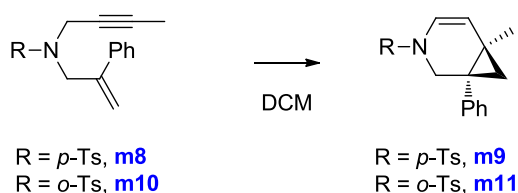
Entry	Solvent	Yields	ee
1	Dioxane/DCM, 5:3	88%	0%
2	Toluene	70%	0%

Table 50 Cycloisomerization of Enyne **m39** in other Solvents than Dichloromethane

Substrate modifications were performed in order to determine whether a higher enantiomeric excess than 62% could be reached. Specifically, the effect of modifications in the linkage (Table 51, entries 1-3) and at the internal position of the alkene (Table 51, entries 4-6) were investigated.

Good yields of **m9** were obtained with IPrAuCl and $\alpha\text{-ICyDAuCl}$ (74% and 78%, respectively, Table 51, entries 1-2). Moreover, a slight improvement of the enantiomeric excess was observed (from 43 to 48% ee) in the case of $\alpha\text{-ICyDAuCl}$ (Table 51, entry 2). With $\beta\text{-ICyDAuCl}$ as the catalyst, the reaction was quantitative and, more importantly, a significant improvement of the enantiomeric excess was observed (from 59 to 80% ee, Table 51, entry 3). Changing the *p*TsN linkage for *o*TsN, however, was detrimental to the enantiomeric excess (Table 51, entries 4-6). With $\alpha\text{-ICyDAuCl}$, the reaction resulted in a very poor asymmetric induction (6% ee, Table 51, entry 5) and with $\beta\text{-ICyDAuCl}$, the enantiomeric excess decreased from 59 to 48% (Table 51, entry 6).

Thus, both positions investigated do impact the stereodifferentiation process, but in opposite ways. While steric hindrance in the linkage seems to be detrimental, the more hindered is the internal position of the alkene, the better.



Entry	R	Catalyst	Loading	Temperature	Time	Yields	ee
1	<i>p</i> -Ts	$\text{IPrAuCl} + \text{AgSbF}_6$	2 mol%	r.t.	15h	74%	0%
2	<i>p</i> -Ts	$\alpha\text{-CyDAuCl} + \text{AgSbF}_6$	5 mol%	40°C	15h	78%	48%

3	p-Ts	β -CyDAuCl + AgSbF ₆	2 mol%	r.t.	15h	100%	80%
4	o-Ts	IPrAuCl + AgSbF ₆	2 mol%	r.t.	15h	80%	0%
5	o-Ts	α -CyDAuCl + AgSbF ₆	5 mol%	40°C	15h	49%	6%
6	o-Ts	β -CyDAuCl + AgSbF ₆	5 mol%	r.t.	15h	68%	48%

Table S1 Effect of Substrate Modifications on the Enantiomeric Excess

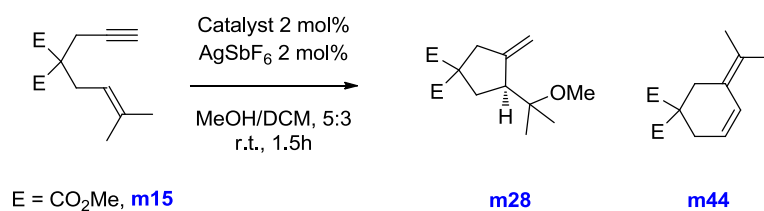
In order to further probe the possibility of asymmetric induction in other types of reactions than the cycloisomerization of 1,6-enynes, methoxy- and hydroxycyclizations were studied.

The methoxy- and hydroxycyclizations of 1,6-enyne **m15** have been reported in the literature by a number of groups, but mostly studied in their asymmetric version by Genêt and Michelet.²⁶³ When it comes to methoxycyclization, however, the reaction was run in the conditions described by Antonio Echavarren, using a 5:3 mixture of MeOH and dichloromethane as the solvent.²⁶⁴ Under those conditions, IPrAuCl afforded the expected product **m28** in excellent yield (93%, Table S2, entry 1). The same yield was obtained with β -ICyDAuCl as the catalyst. Furthermore, **m28** was obtained in excellent enantiomeric excess (94% ee, Table S2, entry 3). This is all the more interesting than only moderate enantiomeric inductions have been reported for this transformation, the best enantiomeric excess having been obtained with a chiral N-heterocyclic carbene under gold(I) catalysis (56% ee).²⁶⁵ The reaction was more sluggish with α -ICyDAuCl (18% of starting material was recovered) and a much lower enantiomeric excess was obtained (30% ee, Table S2, entry 2).

²⁶³ Pradal, A., Chao, C.M., Vitale, M.R., Toullec, P.Y., Michelet, V. *Tetrahedron* **2011**, *67*, 4371-4377; Chao, C.-H., Genin, E., Toullec, P.Y., Genêt, J.P., Michelet, V. *J. Organomet. Chem.* **2009**, *694*, 538-545; Charruault, L., Michelet, V., Taras, R., Gladiali, S., Genêt, J.-P. *Chem. Commun.* **2004**, *7*, 850-851. See also: Matsumoto, Y., Selim, K.B., Nakanishi, H., Yamada, K., Yamamoto, Y., Tomioka, K. *Tetrahedron Lett.* **2010**, *51*, 404-407; Yamada, K., Matsumoto, Y., Selim, K.B., Yamamoto, Y., Tomioka, K. *Tetrahedron* **2012**, *68*, 4159-4165.

²⁶⁴ Nieto-Oberhuber, C., Munoz, M.P., Lopez, S., Jiménez-Núñez, E., Nevado, C., Herrero-Gómez, E., Raducan, M., Echavarren, A.M. *Chem. Eur. J.* **2006**, *12*, 1677-1693.

²⁶⁵ Matsumoto, Y., Selim, K.B., Nakanishi, H., Tamada, K., Yamamoto, Y., Tomioka, K. *Tetrahedron Lett.* **2010**, *51*, 404-407; Yamada, K., Matsumoto, Y., Selim, K.B., Yamamoto, Y., Tomioka, K. *Tetrahedron* **2012**, *68*, 4159-4165.



Entry	Catalyst	Yields	ee m28
1	<i>IPrAuCl</i>	m28 : 93%	0%
2	<i>α-ICyDAuCl</i>	m28 : 77% m44 : 18%	30%
3	<i>β-ICyDAuCl</i>	m28 : 92% m44 : 8%	94%

Table 52 Methoxycyclization of 1,6-Enyne m15

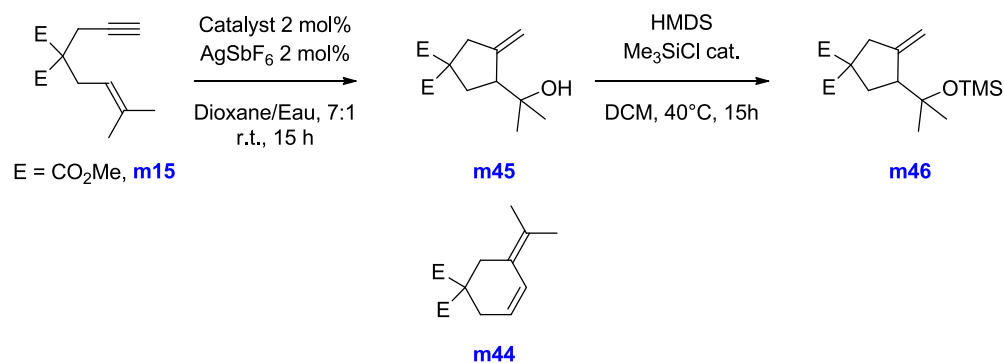
Worthy of note, the 6-membered-ring product **m44** was isolated along with the expected compound **m28** when α - and β -ICyD were used, which is indicative of the protective role of the cavity towards the substrate, in a sense that MeOH may hardly get in the cavity and thus allow the competitive formation of the 6-*endo*-dig cycloisomerization product. It is also worth mentioning that the cycloisomerization of 1,6-enyne **m15** is reported in the literature to afford almost exclusively the 5-membered ring product,²⁶⁶ while in this series of reactions, the 6-membered-ring product was formed (*Table 52, entries 2-3*). To some extent, this is revealing of the influence of the cyclodextrins' cavity on the reaction pathway.

The hydroxycyclization reactions were performed in a mixture of dioxane and water, in accordance to Michelet's work.²⁶⁷ Once again, the reaction with *IPrAuCl* was very efficient, and so was the reaction with β -*ICyDAuCl* (*Table 53, entries 1-2*). Both reactions resulted nonetheless in different outcomes. With *IPrAuCl*, the hydroxycyclization product **m45** was obtained as a sole product whereas with β -*ICyDAuCl*, **m45** was obtained in an almost 1:1 ratio with the cycloisomerization product resulting from an endocyclic skeletal rearrangement **m44**. As in the methoxycyclization reaction, it seems that the cavity partially protects the substrate from the addition of water. Unfortunately, the hydroxycyclization product **m45** and the residual β -*ICyDAuCl* were not separable. As a consequence to this, and for the enantiomeric excess to be measured, the hydroxyl group was protected with HMDS in the presence of a catalytic amount

²⁶⁶ The formation of the 6-membered ring product was observed under platinum and gold catalysis (in 8 and 3% respectively), in dichloromethane as the solvent: Ferrer, C., Raducan, M., Nevado, C., Claverie, C.K., Echavarren, A.M. *Tetrahedron* **2007**, *63*, 6306-6316; Bartolomé, C., Ramiro, Z., Garcia-Cuadrado, D., Pérez-Galan, P., Raducan, M., Bow, C., Echavarren, A.M., Espinet, P. *Organometallics* **2010**, *29*, 951-956.

²⁶⁷ Chao, C.-H., Genin, E., Toullec, P.Y., Genêt, J.-P., Michelet, V. *J. Organomet. Chem.* **2009**, *694*, 538-545.

of TMSCl. Also in this case was the enantiomeric excess excellent and far better than those reported in the literature (**m45** was obtained in 90% *ee* vs. 46% in the literature for this enantiomer, 66% for the other enantiomer).



Entry	Catalyst	Yields	ee m46
1	IPrAuCl	m45 : Quant.	0%
2	β-CyDAuCl	m45 : 48% m44 : 44%	90%
3	No catalyst	No reaction	

Table 53 Hydroxycyclization of 1,6-Enyne **m15**

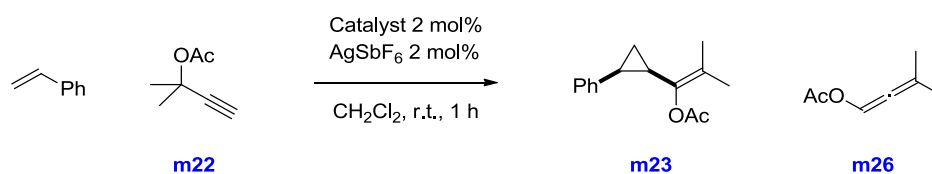
Propargyl ester migrations were also investigated from an asymmetric induction viewpoint. First, the intermolecular cyclopropanation of styrene in the presence of propargyl acetate **m22** was considered, which reaction has been studied by Ohe and Uemura²⁶⁸ and later in its asymmetric version by Toste and Espinet.²⁶⁹ As mentioned earlier, Toste reported manifest ligand effects in the diastereoselectivity of this transformation and proposed the *cis* transition state to be favoured over *trans* due to steric clash between the ligand on gold and the substituent on the incoming olefin.²⁷⁰ IPrAuCl afforded a 87:13 mixture of *cis* and *trans* diastereomers in good yield (68%, Table 54, entry 1). Accordingly to the stereochemical model proposed by Toste, the reaction was totally diastereoselective when α-ICyDAuCl was used (Table

²⁶⁸ Miki, K., Ohe, K., Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505-8513; Miki, K., Ohe, K., Uemura, S. *Tetrahedron Lett.* **2003**, *44*, 2019-1022.

²⁶⁹ Johansson, M.J., Gorin, D.J., Staben, S.T., Toste, F.D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003; Bartolomé, C., Garcia-Cuadrado, D., Ramiro, Z., Espinet, P. *Inorg. Chem.* **2010**, *49*, 9758-9764; Gross, E., Liu, J.H.-C., Toste, F.D., Somorjai, G.A. *Nature Chem.* **2012**, *4*, 947-952; Gross, E., Li, J.H., Alayoglu, S., Marcus, M.A., Fakra, S.C., Toste, F.D., Somorjai, G.A. *J. Am. Chem. Soc.* **2013**, *135*, 3881-3886.

²⁷⁰ See chapter II on OPS-Au(I) catalysts

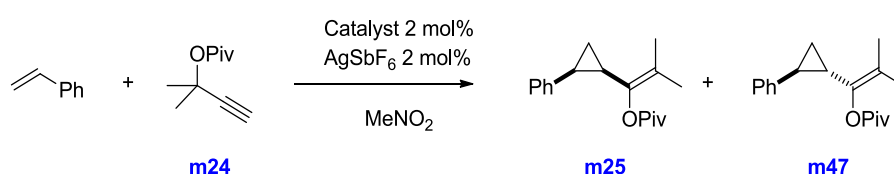
54, entry 2), though the yield was moderate (52%). With β -ICyDAuCl, only low yields of the allenyl acetate were isolated (33%, Table 54, entry 3).



Entry	Catalyst	Yields	cis:trans ratio of m23	m23:m26 ratio	ee of m23
1	IPrAuCl	68%	87:13	1:0	0%
2 ²⁷¹	α -ICyDAuCl	52%	100:0	0.3:1	0%
3	β -ICyDAuCl	33%	-	0:1	-

Table 54 Intermolecular Cyclopropanation of Styrene in the Presence of Propargyl Acetate **m22**

Slightly better results were obtained when propargyl pivalate **m24** was used as the substrate, but both the yields and enantiomeric excesses obtained with NHC-capped cyclodextrins remained low. IPrAuCl gave a 16:1 mixture of *cis* and *trans* products **m25** and **m47** (Table 55, entry 1), which is close to the 20:1 ratio reported by Toste with (*R*)-DTBM-SEGPHOS(AuCl)₂ as the catalyst. Surprisingly, a larger quantity of the *trans* product **m47** was obtained with α -CyDAuCl (3:1 **m25:m47**, Table 55, entry 2) in this case, whereas the reaction was totally diastereoselective with β -ICyDAuCl (Table 55, entry 3). Only 7 and 17% ee were obtained with α - and β -ICyDAuCl catalysts respectively, which is much lower than the 81% ee reported by Toste (Table 55, entries 2-3).



Entry	Catalyst	Temperature	Time	Yields	ee of m25
1	IPrAuCl + AgSbF ₆	r.t.	1.5h	m25 : 64% m47 : 4%	0%
2	α -CyDAuCl + AgSbF ₆	50°C	15h	m25 : 34% m47 : 11%	7%
3	β -CyDAuCl + AgSbF ₆	r.t.	1.5h	m25 : 50% m47 : Traces	17%

²⁷¹ A longer reaction time (overnight) led to degradation, so that the *cis* diastereomer was obtained as a sole product in 9% yield.

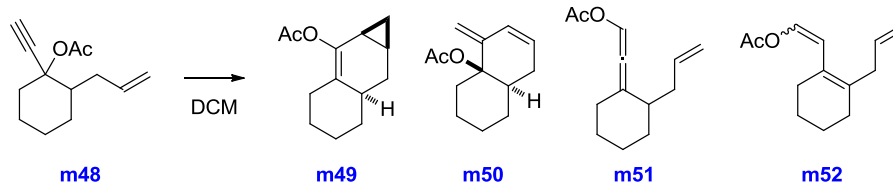
The enantioselective intramolecular cyclopropanation of propargyl acetate **m48** has never been reported in the literature.²⁷² The latter was obtained as a sole product in excellent yield with PtCl₂ as the catalyst (88%).²⁷³ Under gold catalysis, however, several other products were observed, coming from the competitive 1,3 migration of the propargyl acetate.²⁷⁴

Here, the reaction was complete within 5 minutes at room temperature with IPrAuCl but a significant amount of allene was formed (0.5:1.3 C:A with C: cyclopropanation products and A: products arising from 1,3 migration, Table 56, entry 1). It was possible to increase the amount of cyclopropanation product by running the reaction at 40°C and over a longer period of time (42% of cycloisomerization product vs. 21% a r.t., Table 56, entry 2), though the global yield was significantly lowered. The reaction with α -ICyDAuCl needed to be run at 40°C with 5 mol% of catalyst and afforded the cyclopropanation product in low yield (22%, Table 56, entry 3). With β -ICyDAuCl, as it was the case with IPrAuCl, the amount of cyclopropanation product could be increased at 40°C (49% vs. 16% at r.t., Table 56, entries 4-5) at the expense of the global yield of the reaction (49% vs. 68% at r.t.). Surprisingly, a better asymmetric induction was observed with α -ICyDAuCl than with β -ICyDAuCl in this case (36 vs. 10% ee, respectively, Table 56, entries 3 and 5). The effect of α - and β -cavities may thus be reversed depending on the structure of the substrate and/or type of reaction.

²⁷² For the racemic intramolecular cyclopropanation of propargyl acetate **m48**, see: Moreau, X., Goddard, J.-P., Bernard, M., Lemièrre, G., Lopez-Romero, J.M., Mainetti, E., Marion, N., Mouriès-Mansuy, V., Thorimbert, S., Fensterbank, L., Malacria, M. *Adv. Synth. Catal.* **2008**, *350*, 43-48; Harrack, Y., Makhlouf, M., Azzaro, S., Mainetti, E., Lopez-Romero, J.H., Cariou, K., Gandon, V., Goddard, J.P., Malacria, M., Fensterbank, L. *J. Organomet. Chem.* **2011**, *696*, 388-399.

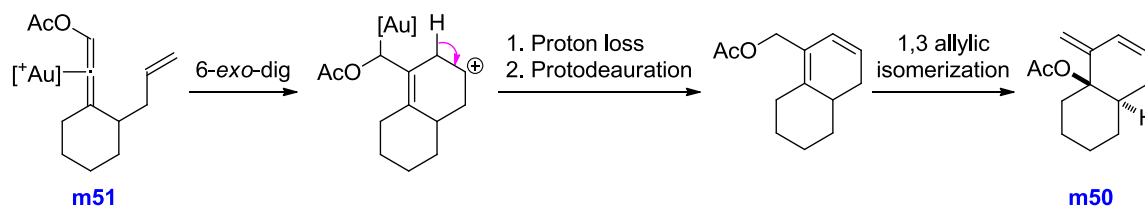
²⁷³ Moreau, X., Goddard, J.-P., Bernard, M., Lemièrre, G., Lopez-Romero, J.M., Mainetti, E., Marion, N., Mouriès, V., Thorimbert, S., Fensterbank, L., Malacria, M. *Adv. Synth. Catal.* **2008**, *350*, 43-48.

²⁷⁴ Harrak, Y., Makhlouf, M., Azzaro, S., Mainetti, E., Lopez-Romero, J.M., Cariou, K., Gandon, V., Goddard, J.-P., Malacria, M., Fensterbank, L. *Journal of Organometallic Chemistry* **2011**, *696*, 388-399.



Entry	Catalyst	Loading	T	Time	Global Yield	m49:m50:m51:m52 ratio	Yield of m49	ee of m49
1	IPrAuCl + AgSbF ₆	2 mol%	r.t.	5 min	75%	0.5: 0.3:1:0	21%	
2			40°C	15h	42%	1:0:0:0	42%	0%
3	α-CyDAuCl + AgSbF ₆	5 mol%	40°C	15h	22%	1:0:0:0	22%	36%
4	β-CyDAuCl + AgSbF ₆	2 mol%	r.t.	1h	68%	0.3:0:1:0	16%	
5			40°C	1h	49%	1:0:0:0	49%	10%

Table 56 Intramolecular Cyclopropanation of Propargyl Acetate **m48**



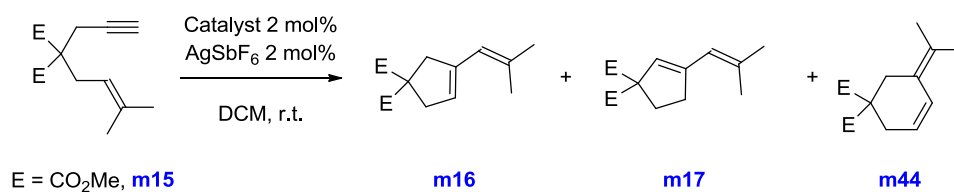
Scheme 161 Mechanism Proposal for the Formation of **m50**

Another possible added value of the cyclodextrins' cavity except for asymmetric induction would be a modification of the reaction pathway and thus a modification of the outcome of the reaction. Although the formation of the 6-membered-ring product was observed by Echavarren under gold and platinum catalysis (in 3 and 8% yield respectively),²⁷⁵ malonate **m15** most often leads to the formation of isomeric 5-membered ring products **m16** and **m17**.²⁷⁶

²⁷⁵ Ferrer, C., Raducan, M., Nevado, C., Claverie, C.K., Echavarren, A.M. *Tetrahedron* **2007**, *63*, 6306-6316; Bartolomé, C., Ramiro, Z., Garcia-Cuadrado, D., Pérez-Galan, P., Raducan, M., Bow, C., Echavarren, A.M., Espinet, P. *Organometallics* **2010**, *29*, 951-956.

²⁷⁶ Nieto-Oberhuber, C., Munoz, M.P., Bunuel, E., Nevado, C., Cardenas, D.J., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406; Nieto-Oberhuber, C., Lopez, S., Munoz, M.P., Cardenas, D.J., Bunuel, E., Nevado, C., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148; Nieto-Oberhuber, C., Munoz, M.P., Lopez, S., Jiménez-Nunez, E., Nevado, C., Herrero-Gomez, E., Raducan, M., Echavarren,

The same selectivity for the 5-membered-ring products was observed with IPrAuCl and α -ICyDAuCl (1:0.7 **m16:m17**, *Table 57*, entries 1-2), yet the yield was significantly lower with the latter (52% with α -ICyDAuCl vs. 88% with IPrAuCl). Interestingly, and as previously observed in methoxy- and hydroxycyclization reactions, β -ICyDAuCl was on the contrary selective toward the formation of the 6-membered-ring product **m44** (1:3.3 **m16:m44**, 63% global yield, *Table 57*, entry 3). Thus, the cavity does have an effect on the reaction pathway and the outcome of the reaction.



Entry	Catalyst	Reaction time	Yields	m16:m17:m44 ratio
1	IPrAuCl	3 h	88%	1:0.7:0
2	α -CyDAuCl	15 h	52%	1:0.7:0
3	β -CyDAuCl	15 h	63%	1:0:3.3

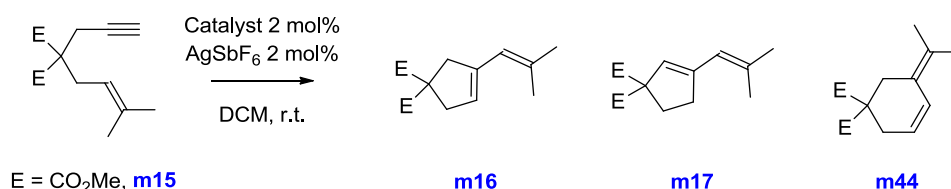
Table 57 Cyclisomerization of 1,6-enyne **m15**

In order to see whether modifications on the catalysts may have an impact on selectivity and whether the selectivity in favour of the 6-membered-ring product could be improved further, other NHC-capped cyclodextrins were tested.

Very good to quantitative yields were obtained in all cases. Only β -BiCyDAuCl, however, was selective in for the 6-membered-ring product **m44** (*Table 58*, entry 2). More specifically, the selectivity between 5-*exo*-dig and 6-*endo*-dig cyclizations was almost identical with both β -ICyDAuCl and β -BiCyDAuCl (1:3.3 vs. 1:3.4, respectively). On the contrary, all α -cyclodextrin-based catalysts gave selective reactions in favour of the 5-membered-ring products (*Table 58*, entries 1, 3 and 4).

Thus, modifications on the catalysts have little impact on the selectivity of the reaction, that seems to be rather dependent on the α or β character of the cyclodextrin in that α -cyclodextrin-based catalysts were selective for the 5-membered-ring products **m16** and **m17** whereas β -cyclodextrin-based catalysts were selective for the 6-membered-ring product **m44**. Once again, initial α - and β -ICyDAuCl were kept as catalysts of choice.

A.M. *Chem. Eur. J.* **2006**, *12*, 1677-1693; Smirnova, E.S., Echavarren, A.M. *Angew. Chem. Int. Ed.* **2013**, *52*, 9023-9026.



Entry	Catalyst	Loading	Temperature	Reaction time	Yields	<i>m16:m17:m44</i> ratio
1	α -BiCyDAuCl + AgSbF ₆	2 mol%	r.t.	15h	87%	1:0.3:0.2
2	β -BiCyDAuCl + AgSbF ₆	2 mol%	r.t.	15h	88%	1:0.7:5.7
3	α -TiCyDAuI + AgSbF ₆	2 mol%	r.t.	15h	100%	1:0.8:0.1
4	α -TiCyDAuSbF ₆	2 mol%	r.t.	15h	78%	1:0.4:0.2

Table 58 Influence of the Catalyst on the Selectivity in the Cycloisomerization of 1,6-Enyne **m15**

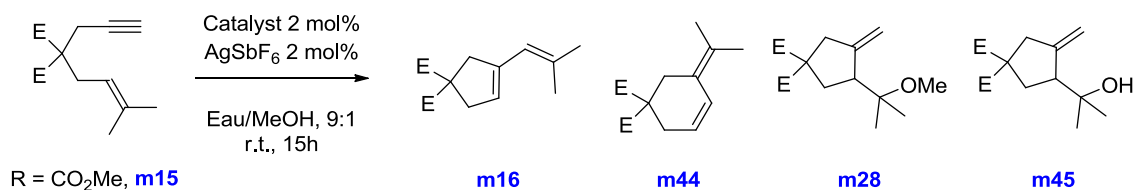
To further investigate the effect of cyclodextrins' cavity on selectivity, a series of competitive reactions involving the competitive additions of various nucleophiles were run.

First of all, the cyclization of enyne **m15** was performed in a 9:1 mixture of water and methanol (that is the minimum of MeOH required for the substrate (oil) and NHC-capped cyclodextrins (foams) to be introduced into the reaction mixture as clear solutions).

With IPrAuCl, the reaction resulted in low conversion (68% of starting material recovered), most probably due to the poor solubility of the catalyst in those conditions (Table 59, entry 1). Methoxy- and hydroxycyclization products **m28** and **m45** were isolated in a 1:3.8 ratio. Since in regard to their amount of substance, MeOH and water were introduced in a 1:2.3 ratio, it seems that the addition of water is preferred over that of MeOH in a sense that the addition of one molecule of MeOH corresponds the addition of ~1.6 water molecules.

The reaction with α -ICyDAuCl was also sluggish (41% of starting material recovered, Table 59, entry 2). Hydroxy- and methoxycyclization products **m28** and **m45** were obtained in almost the same proportions as with IPrAuCl but cycloisomerization products **m16** and **m44** were also isolated in this case, with the selectivity being in favour of the 5-membered-ring product, accordingly to what was previously observed. With β -ICyDAuCl, the reaction went to completion (Table 59, entry 3). Again, hydroxy- and methoxycyclization products **m28** and **m45** were isolated in similar proportions and, as for α -ICyDAuCl, the cycloisomerization process did occur to some extent. In this case, however, none of the 5-membered-ring was formed, whereas the 6-membered-ring product was isolated in good yield (57%).

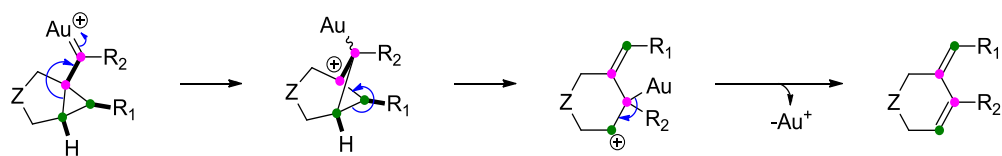
As previously observed, both α - and β -ICyDAuCl catalysts thus protected to some extent the substrate from the addition of MeOH and water and this effect was enhanced in the case of β -ICyDAuCl. The diminished reactivity of α -ICyDAuCl may arise from the size of its cavity, which is smaller than that of β -ICyDAuCl. The cavity-dependent selectivity between 5-*exo*-dig and 6-*endo*-dig cyclizations was also confirmed.



Entry	Catalyst	m15	m16	m44	m28	m45
1	IPrAuCl	68%	-	-	5%	19%
2	α -CyDAuCl	41%	7%	2%	6%	20%
3	β -CyDAuCl	-	-	57%	6%	22%

Table 59 cycloisomerization of 1,6-Enyne **m15** in a 9:1 Mixture of Water and MeOH

Worthy of note, the addition of either water or methanol invariably occurs on the intermediate resulting from 5-*exo*-dig cyclization, even when the reaction is run with β -ICyDAuCl, thus confirming that the 6-membered-ring product arises from the 5-*exo*-dig cyclization process followed by endocyclic skeletal rearrangement of the intermediate so formed (Scheme 165).

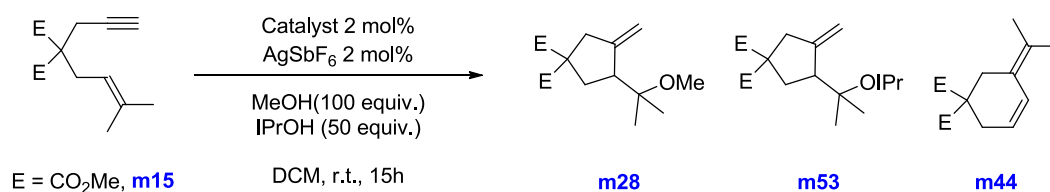


Scheme 162 Endocyclic Skeletal Rearrangement of 1,6-Enynes

In order to compare the reactivity of methanol to that of a secondary alcohol (IPrOH) and a different primary alcohol (BnOH), enyne **m15** was reacted in the presence of methanol and either alcohol.

Specifically, a 2:1 ratio of MeOH and IPrOH was used. With IPrAuCl, the reaction led to a mixture of both addition products **m28** and **m53** but was nonetheless clearly selective in favour of the addition of the smaller and thus more nucleophilic methanol (Table 60, entry 1). The latter also added preferentially over IPrOH when the reaction was run with β -ICyDAuCl. In this case, however, the relative amount of product resulting from the addition of IPrOH slightly increased,

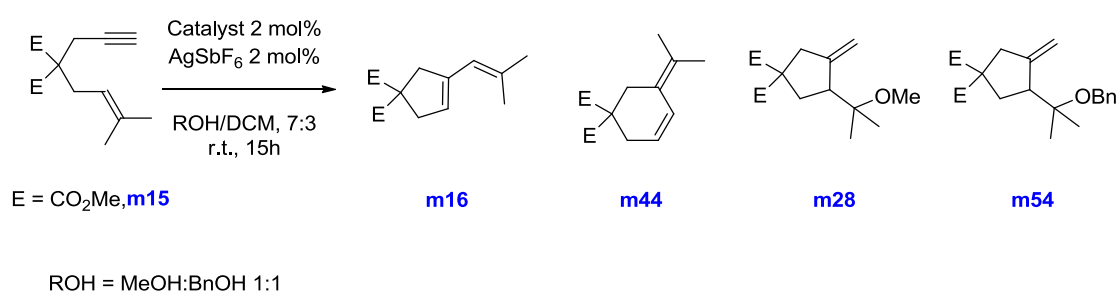
which would mean that the cavity of the cyclodextrin somewhat helps the addition of IPrOH over that of MeOH. Both alcohols have similar polarities but one can imagine that the encapsulation of IPrOH is facilitated by hydrophobic interactions between its lipophilic alkyl chain and the inside of the cavity (*Table 60, entry 2*).



Entry	Catalyst	Yields	<i>m28:m53</i> ratio
1	IPrAuCl	m28 : 88% m53 : 9%	9.8:1
2	β-CyDAuCl	m28 : 65% m53 : 10% m44 : 9%	6.5:1

Table 60 Competitive Nucleophilic Additions of MeOH and IPrOH to m15

Comparable results were obtained when MeOH was mixed with benzyl alcohol. As expected with IPrAuCl, the reaction was selective in favour of MeOH addition (*Table 61, entry 1*). The amount of product resulting from the addition of benzyl alcohol increased when the reaction was run with β-ICyDAuCl (*Table 61, entry 2*). One may wonder whether benzyl alcohol could add preferentially *via* π-stacking interactions with the perbenzylated cyclodextrin. Overall, it seems that the addition of less nucleophilic alcohols than MeOH may be favoured in the presence of β-ICyDAuCl.



Entry	Catalyst	Yield of <i>m16</i>	Yield of <i>m44</i>	Yield of <i>m28</i>	Yield of <i>m54</i>	Global Yield	<i>m28:m54</i> ratio
1	IPrAuCl	2%	0%	53%	27%	82%	2:1
2	β -CyDAuCl	2%	44%	13%	12%	79%	1:1

Table 61 Competitive Nucleophilic Additions of MeOH and BnOH to *m15*

We then turned our attention toward the intramolecular addition of oxygen nucleophiles. For this purpose, allenol *m55* was chosen as the substrate. The intramolecular hydroalkoxylation of this compound has been widely investigated with various metals (Pt, Au, Ag, Sn, Zn) by Widenhoefer, Hii and Espinet, mostly in its enantioselective version, and both excellent yields and enantiomeric excesses (>90%) have been reported. From a regioselectivity standpoint, the 5-membered-ring product was predominantly formed in all cases.²⁷⁷

IPrAuCl led to the formation of an almost 1:1 mixture of *m56* and *m58* (41% global yield, Table 62, entry 1). The latter has never been reported in the literature and would result from the autocondensation of the 6-membered-ring gold intermediate (Scheme 163).²⁷⁸ β -ICyDAuCl gave *m58* in 50% yield along with some hydration product *m59* (14%). Thus, the cavity of the cyclodextrin seems to favour the 6-*endo*-dig cyclization process (Table 62, entry 2). With both catalysts, the 6-membered-ring product seems to react further in the presence of gold to give the corresponding dimer *m58*.

Upon the addition of 5 equivalents of EtOH, a complete change in the selectivity of the reaction with IPrAuCl was observed (Table 62, entry 3), the 5-membered-ring product *m56* now being obtained exclusively in very good yield (87%). No product arising from the addition of ethanol was observed, which may be explained by a faster intramolecular reaction. With β -ICyDAuCl also, the 5-membered-ring product was now formed but in a much lower yield (14%, Table 62, entry 4) than with IPrAuCl. The major product in this case was the one resulting from the addition of ethanol (*m57*, 46%).

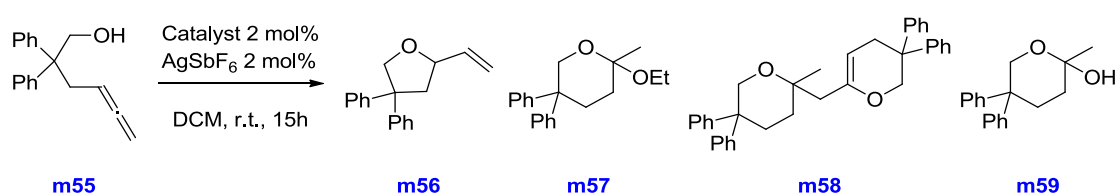
²⁷⁷ Zhang, Z., Liu, C., Knider, R.E., Han, X., Qian, H., Widenhoefer, R.A. *J. Am. Chem. Soc.* **2006**, *128*, 9066-9073; Aikawa, K., Kojima, M., Mikami, K. *Adv. Synth. Catal.* **2010** DOI: 10.1002/adsc.201000672; Zhang, Z., Widenhoefer, R.A. *Angew. Chem. Int. Ed.* **2007**, *46*, 283-285; Gramage-Doria, R., Bellini, R., Pintjema, J., Reek, J.N.H. *Chem. Cat. Chem.* **2013**, *5*, 1084-1087; Arbour, J.L., Rzepa, H.S., Contieras-Garcia, J., Adrio, L.A., Barreiro, E.M., Hii, K.K. *Chem. Eur. J.* **2012**, *18*, 11317-11324; Arban, J.L., Rzepa, M.S., White, A.J.P., Hii, K.K. *Chem. Commun.* **2009**, 7125-7127; Bartolomé, C., Garcia-Cuadrado, D., Ramiro, Z., Espinet, P. *Inorg. Chem.* **2010**, *49*, 9758-9764; Brown, T.J., Weber, D., Gagné, M.R., Widenhoefer, R.A. *J. Am. Chem. Soc.* **2012**, *134*, 9134-9137; Bartolomé, C., Garcia-Cuadrado, D., Ramiro, Z., Espinet, P. *Organometallics* **2010**, *29*, 3589-3592.

²⁷⁸ The condensation of the starting material onto the 6-membered-ring product was reported in the literature under zinc catalysis: Arban, J.L., Rzepa, H.S., White, A.J.P., Hii, K.K. *Chem. Commun.* **2009**, 7125-7127.

In order to rationalize those results, one can formulate the following hypotheses:

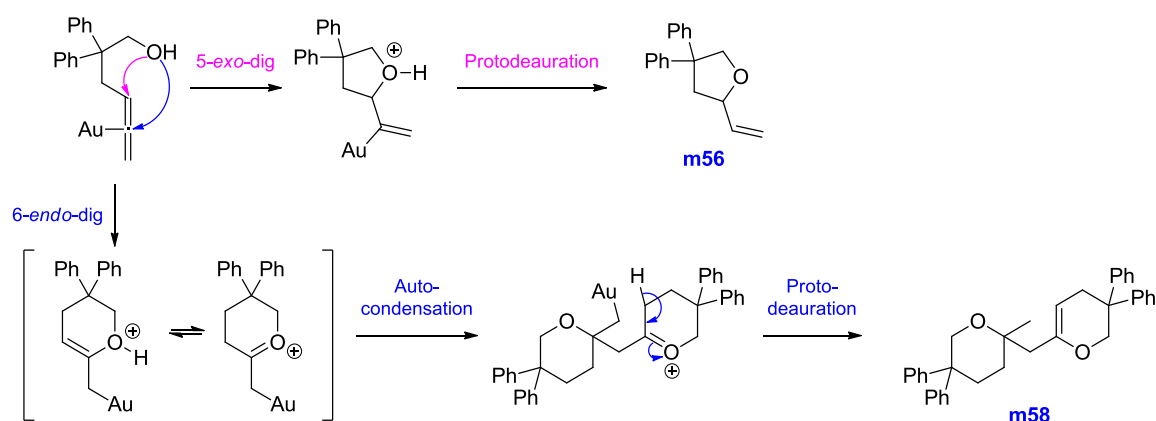
-the addition of EtOH somewhat modified the nature (polarity) of the solvent, under which conditions the formation of the 5-membered-ring product **m56** is favoured over that of the 6-membered-ring product.

-inside the cavity of the cyclodextrin, the proportion of ethanol might be lower, so that the 6-membered ring is still preferentially formed. However, EtOH is to some extent encapsulated into the cyclodextrin cavity and is a much stronger nucleophile than the 6-membered-ring gold intermediate, so that the addition of EtOH is now favoured over the dimerization process.



Entry	Catalyst	EtOH (5 equiv.)	m56	m57	m58	m59
1	IPrAuCl	NO	20%	-	21%	Traces
2	β -CyDAuCl	NO	-	-	50%	14%
3	IPrAuCl	YES	87%	-	-	-
4	β -CyDAuCl	YES	14%	46%	-	-

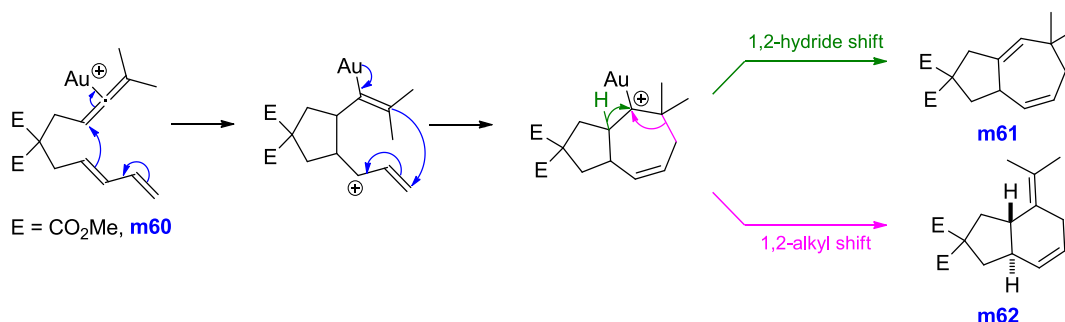
Table 62 Intramolecular Hydroalkoxylation of Allenol **m55** with or without Ethanol



Scheme 163 Proposed Mechanism for the Formation of **m56** and **m58**

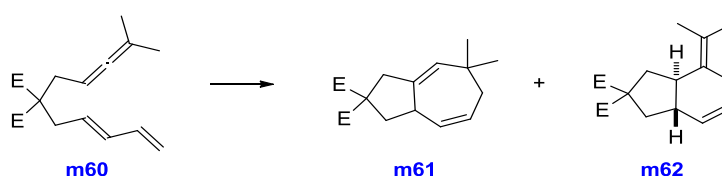
The reaction of allenediene **m60** may evolve along two different pathways as a function of the electronic properties of the ligand coordinated to gold. With σ -donating ligands, a 1,2-

hydride shift leads to the formation of **m61** whereas π -acid ligands favour ring contraction via a 1,2-alkyl migration process toward the formation of **m62** (see *Scheme 167*).²⁷⁹



Scheme 164 Proposed Mechanism for the Reaction of Allenediene m60

Accordingly, the strongly electron-donating IPrAuCl was reported to afford exclusively product **m61** arising from [4+3] cycloaddition (*Table 63, entry 1*). While with α -ICyDAuCl, an almost 1:1 ratio of both cycloaddition products **m61** and **m62** was obtained (*Table 63, entry 2*), the [3+2] cycloaddition product **m62** became predominant when the reaction was run with β -ICyDAuCl (1:2.3 **m61**: **m62**, *Table 63, entry 3*). Thus, the cavity does have an influence on the electron-donating ability of the gold-carbene. Especially, both α - and β -cyclodextrins lowered the electron-donating ability of the carbene ligand. One might hypothesize that this actually is a steric effect, in that a non-linearity of the P-Au-C angle and thus a diminished π -back donation from gold may be imposed by the cavity of both cyclodextrins.



Entry	Catalyst	Loading	Solvent	Temperature	Reaction time	Yields	m61 : m62 ratio
1	IPrAuCl ²⁸⁰ + AgSbF ₆	10 mol%	DCM	r.t.	30 min	91%	1: 0
2	α -CyDAuCl + AgSbF ₆	5 mol%	DCE	80°C	2h	76%	1:1.3

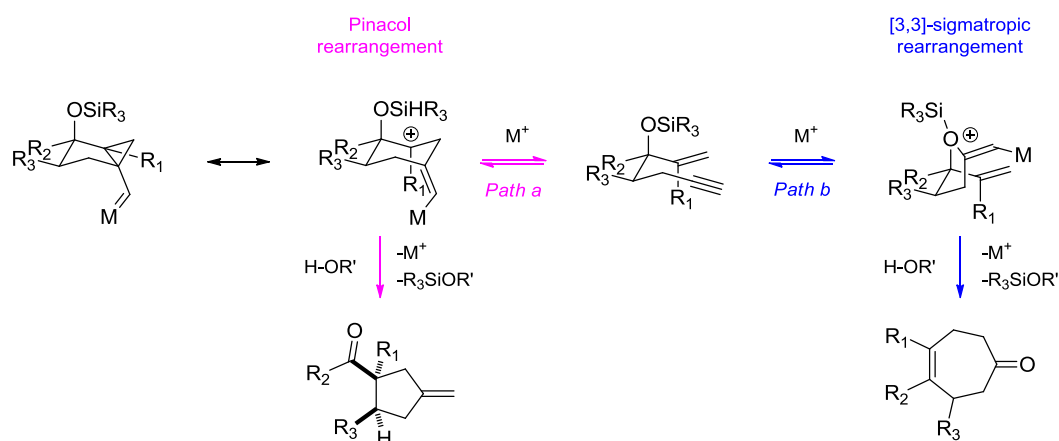
²⁷⁹ Trillo, B., Lopez, F., Montserrat, S., Ujaque, G., Castedo, L., Lledos, A., Mascarenas, J.L. *Chem. Eur. J.* **2009**, *15*, 3336-3339; Mauleon, P., Zeldin, R.M., Gonzalez, A.Z., Toste, F.D. *J. Am. Chem. Soc.* **2009**, *131*, 6348-6349; Benitez, D., Tkatchouk, E., Gonzalez, A.Z., Goddard III, W.A., Toste, F.D. *Org. Lett.* **2009**, *11*, 4798-4801.

²⁸⁰ Beatriz Trillo, Fernando Lopez, Sergi Montserrat, Gregori Ujaque, Luis Castedo, Agusti Lledos, and Jose L. Mascarenas, *Chem. Eur. J.* **2009**, *15*, 3336-3339.

3 β -CyDAuCl + AgSbF₆ 5 mol% DCM 40°C 15h 79% 1:2.3

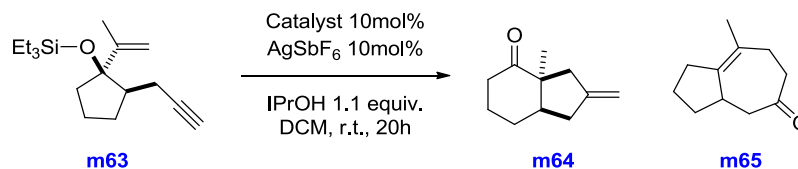
Table 63 [4+3] vs. [3+2] Cycloadditions of Allenediene **m60**

Under gold catalysis, 3-silyloxy-1,6-enynes lead to either a carbocyclization and subsequent pinacol rearrangement in the presence of electron-donating ligands (Scheme 168, Path a) or a heterocyclization followed by a Claisen rearrangement when an electron-withdrawing ligand is bound to gold (Scheme 168, Path b).²⁸¹



Scheme 165 Reactivity of 3-silyloxy-1,6-enynes in the Presence of Electron-Donating Ligands (Path a) or Electron-Withdrawing Ligands (Path b)

As expected, IPrAuCl reacted toward the preferential formation of **m64** (1:0.5 **m64**:**m65**, Table 64, entry 2), which selectivity was reversed with α -ICyDAuCl as the catalyst (0.5:1 **m64**:**m65**, Table 64, entry 3). β -ICyDAuCl led to an almost 1:1 ratio between **m64** and **m65** (Table 64, entry 4). Thus, the cavity of both cyclodextrins lower the electron-donating character of the gold carbene but from the comparison of the latter results with those obtained with allenediene **m60**, it seems that this effect is substrate as well as cavity-dependent.



Entry	Catalyst	Yield of m64	Yield of m65	Global Yield	m64 : m65 ratio
1	AgSbF ₆ alone	0%	11%	11%	0:1

²⁸¹ Baskar, B., Bae, H.J., Ar, S.E., Cheong, J.Y., Rhee, Y.H., Duschek, A., Kirsch, S.F. *Org. Lett.* **2008**, *10*, 2605-2607; Alcarazo, M., Stork, T., Anoop, A., Thiel, W., Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2542-2546.

2	IPrAuCl	33%	17%	50%	1:0.5
3	α CyDAuCl	17%	33%	50%	0.5:1
4	β CyDAuCl	28%	39%	67%	1:1.4

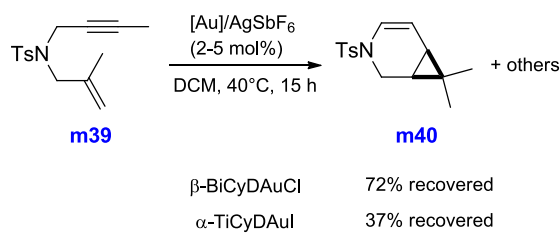
Table 64 Pinacol vs. [3,3]-Sigmatropic Rearrangement of **m63**

II. Conclusions

To conclude, it has been shown that the encapsulation of gold in NHC-capped cyclodextrins does not prevent the metal from being reactive. The effects of the size and chirality of the cavity on the reactivity of the gold carbene were studied in comparison to the results obtained with IPrAuCl. Specifically, the possibility of a stereodifferentiating effect was assessed in various transformations. Good to excellent enantiomeric excesses were obtained in the cycloisomerization of 1,6-enynes (60-80% *ee*) and hydroxy- and methoxycyclization reactions (>90% *ee*). Poorer results, however, were obtained in the rearrangement of propargyl acetates, with enantiomeric excesses ranging from 0 to 36%. β -cyclodextrin-based catalysts were usually responsible for better asymmetric inductions, though this trend was reversed in the rearrangement of propargyl acetate and subsequent intramolecular cyclopropanation reaction, thus suggesting a substrate and/or reaction-dependence. It has also been demonstrated that the cavity of the cyclodextrin may induce a bifurcation of the reaction pathway so that the outcome of the reaction is modified. Especially, the 6-*endo*-dig cyclization seems to be favoured inside the cavity of β -cyclodextrins, as illustrated in the reaction of 1,6-enyne **m15** or allenol **m55**. Besides, NHC-capped cyclodextrins protected to some extent the substrate from the addition of nucleophiles such as water or methanol and favoured the addition of the less nucleophilic IPrOH and BnOH. Finally, reactions evolving through alternative pathways as a function of the electronic properties of the ligand borne by the gold centre were indicative of a diminished electron donation from the gold carbene.

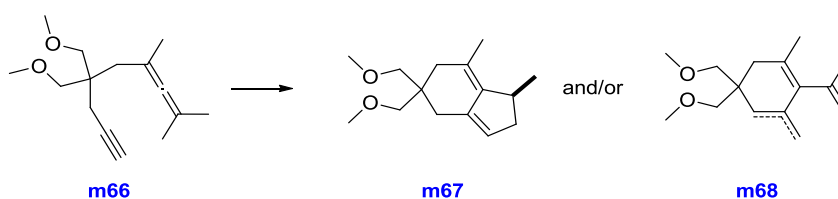
III. Perspectives

Future work will be focussed on the preparation of stable cationic catalysts in order avoid the use of a potentially competitive silver salt. The catalysts might also be recycled. Efforts have been made in this regard. For instance, some unreacted catalyst has been recovered in the cycloisomerization of enyne **m39** (Scheme 169). In principle, cationic complexes could be converted back into the gold chloride derivatives by the addition of tetrabutylammonium chloride (TBACl).



Scheme 166 Partial Recovery of NHC-Capped Cyclodextrin-Gold(I) Complexes in the Cycloisomerization of 1,6-Enyne m39

In parallel, the behaviour of NHC-capped cyclodextrins in other types of reactions will be explored. For example, the cycloisomerization of allenynes will be considered.²⁸²



Entry	Catalyst	Yield of <i>m67</i>	Yield of <i>m68</i>
1	AuCl ₃ 1 mol%	80%	Traces
2	[Au(PPh ₃)SbF ₆] 1 mol%	0%	70%

Table 65 Catalyst-Dependent Selectivity in the Cycloisomerization of Allenynes

²⁸² Lemière, G., Gandon, V., Agenet, N., Goddard, J.-P., de ozak, A., Aubert, C., Fensterbank, L., Malacria, M. *Angew. Chem. Int. Ed.* **2006**, 45, 7596-7599.

Experimental Part

General considerations

The nomenclature used is that recommended by IUPAC.

Reactions

All reactions were carried out in heat gun-dried glassware under dry argon atmosphere.

All commercially available compounds were used as received when not precised.

Purifications

THF and CH₂Cl₂ were purified either by distillation over Na/benzophenone (THF) or CaH₂ (CH₂Cl₂), or with the solvent purification system MB SPS-800. Toluene was distilled from sodium-potassium alloy. They all were transferred under argon atmosphere.

Thin Layer Chromatography (TLC) was performed on Merck 60 F254 silica gel an Merck Geduran SI 60 A silica gel (35-70 mm) was used for flash chromatography.

Analyses

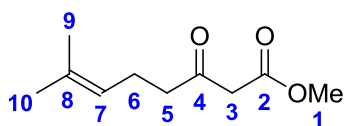
Melting points **F** were measured on a Bibby Stuart Scientific melting point apparatus SMP3.

IR: spectra were recorded on a Tensor 27 ATR diamante PIKE FT-IR Spectrometer. Wavenumbers (ν) are given in cm⁻¹.

NMR: spectra were recorded on Bruker B-ACS 60 300 MHz and 400 MHz spectrometers in CDCl₃. Chemical shifts (δ) are given in ppm relative to TMS. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale (CDCl₃ : δ C = 77.16 ppm ; Residual CHCl₃ in CDCl₃ : δ H = 7.26 ppm). Signals were attributed with the help of ¹H, ¹³C, COSY, HSQC, HMBC and NOESY experiments.

LRMS and HRMS: FTMS was performed by the Mass Spectrometry group of the IPCM.

Methyl-7-methyl-3-oxooct-6-enoate ^{s25}²⁸³



C₁₀H₁₆O₃
184.2 g.mol⁻¹
Yellow oil
76%

Methyl acetoacetate (0.94 mL, 99%, 8.6 mmol, 1.0 equiv.) was added very slowly to a suspension of NaH (517 mg, 60% disp. in oil, 12.9 mmol, 1.50 equiv.) in THF (14.0 mL) cooled at 0°C. At this temperature, the mixture was stirred for 10 min and *n*-BuLi (4.1 mL, 2.3 M, 9.5 mmol, 1.1 equiv.) was slowly added. At the same temperature, the mixture was stirred for additional 10 min and 1-bromo-3-methyl-2-butene (1.2 mL, 90%, 9.5 mmol, 1.1

equiv.) was quickly added. After additional 5 min stirring at 0°C, the completion of the reaction was monitored by TLC (*n*-Pent/Et₂O, 90/10). The mixture was quenched by the careful addition of 1 M HCl (20 mL) and extracted with Et₂O (3 x 10 mL), and the combined organic extracts were washed with saturated NaHCO₃ (1 x 15 mL) solution and brine (1 x 15 mL). The resulting organic layer was dried over MgSO₄, filtered and concentrated under vacuum. Pure methyl-7-methyl-3-oxooct-6-enoate was isolated as a yellow oil (1.20 g, 6.50 mmol, 76%) by flash chromatography on silica gel (*n*-Pent/Et₂O, 90:10). A mixture of ketone and enol tautomers in a 10:1 ratio was obtained.

R_f = 0.15 (*n*-Pent/Et₂O, 90:10).

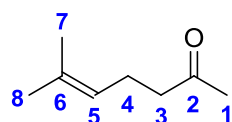
IR (neat): $\tilde{\nu}$ = 2922 (ν_{C-H alkyl}), 1716 (ν_{C=O}), 1634 (ν_{C=C}), 1440 (δ_{C-H alkyl}), 832 (δ_{C-H vinyl}).

¹H NMR (CDCl₃, 300 MHz): δ 12.00 (s, 1H, OH of the enol tautomer), 5.10-5.00 (m, 1H, H-7), 4.98 (s, 1H, H-3 of the enol tautomer), 3.73 (s, 3 H, H-1), 3.44 (s, 2 H, H-3), 2.55 (t, ³J₅₋₆ = 7.5 Hz, 2H, H-5), 2.27 (q, ³J₆₋₅ = ³J₆₋₇ = 7.5 Hz, 2H, H-6), 1.67 (s, 3 H, H-10), 1.42 (s, 3 H, H-9).

¹³C NMR (CDCl₃, 100 MHz): δ 202.6 (C-4), 167.8 (C-2), 133.1 (C-8), 122.3 (C-7), 52.5 (C-1), 49.2 (C-3), 43.2 (C-5), 25.8 (C-9), 22.3 (C-6), 17.8 (C-10).

6-methylhept-5-en-2-one ^{s26}²⁸⁴

²⁸³ Litt.: Taber, D.F., Silverberg, L.J., Robinson, E.D. *J. Am. Chem. Soc.* **1991**, *113*, 6639.



C₈H₁₄O
126.2 g.mol⁻¹
Orange oil
85%

The crude ketoester **s25** (10.5 g, 56.9 mmol, 1.00 equiv.) was dissolved in DMSO (37.5 mL). Distilled water (1.0 mL, 56.9 mmol, 1.0 equiv.) and LiCl (4.88 g, 99%, 114 mmol, 2.00 equiv.) were added, and the reaction was heated at reflux ($T_{\text{DMSO}}^{\text{b}} = 191^{\circ}\text{C}$) for 2 h. After the completion of the reaction was monitored by TLC (PE/Et₂O, 70:30), the mixture was allowed to cool to room temperature and quenched with distilled water (40 mL). The aqueous layer was extracted with Et₂O (4 x 15 mL) and the combined organic extracts were washed with distilled water (2 x 30 mL) and brine (1 x 30 mL). The resulting organic layer was dried over MgSO₄, filtered and concentrated under vacuum. Crude 6-methylhept-5-en-2-one was isolated as an orange oil (6.09 g, 48.4 mmol, 85%).

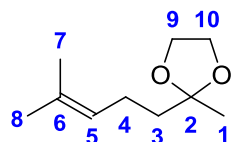
$R_f = 0.26$ (*n*-Pent/Et₂O, 90:10).

IR (neat): $\tilde{\nu} = 2921, 2855$ ($\nu_{\text{C-H alkyl}}$), 1714 ($\nu_{\text{C=O}}$), 1635 ($\nu_{\text{C=C}}$), 1452 ($\delta_{\text{C-H alkyl}}$), 833 ($\delta_{\text{C-H vinyl}}$).

¹H NMR (CDCl₃, 300 MHz): δ 5.08-5.02 (t, $^3J_{5-4} = 7.4$ Hz, 1H, H-**5**), 2.44 (t, $^3J_{3-4} = 7.4$ Hz, 2H, H-**3**), 2.23 (q, $^3J_{4-5} = ^3J_{4-3} = 7.4$ Hz, 2H, H-**4**); 2.20 (s, 3H, H-**1**), 1.67 (s, 3H, H-**8**), 1.60 (s, 3H, H-**7**).

¹³C NMR (CDCl₃, 75 MHz): δ 208.7 (C-**2**), 132.7 (C-**6**), 122.7 (C-**5**), 43.7 (C-**3**), 29.9 (C-**1**), 25.6 (C-**7**), 22.6 (C-**4**), 17.6 (C-**7**).

2-methyl-2-(4-methylpent-3-en-1-yl)-1,3-dioxolane **s20**²⁸⁵



C₁₀H₁₈O₂
170.2 g.mol⁻¹
Yellow oil
40%

To the crude ketone **s26** (6.09 g, 48.4 mmol, 1.00 equiv.) were successively added trimethyl orthoformate (10.6 mL, 99%, 96.8 mmol, 2.00 equiv.), ethylene glycol (8.1 mL, 99.8%, 62 mmol, 3.0 equiv.) and a catalytic amount of *p*-toluenesulfonic acid (383 mg, 98.5%, 4.50 mol%). After 15 min, the completion of the reaction was monitored by TLC (PE/Et₂O, 95:5) and the mixture was quenched with saturated NaHCO₃ solution (20 mL). The aqueous layer was extracted with Et₂O (3 x 5 mL) and the combined organic extracts were washed with brine (1 x 10 mL), dried over MgSO₄ and filtered. Solvent evaporation under reduced pressure gave crude acetal, which was purified by flash chromatography on silica gel (PE/Et₂O, 95:5 → 50:50) to afford a yellow oil (3.29 g, 19.4 mmol, 40%) as the pure product.

²⁸⁴ Litt.: Michrowska, A., Gulajski, L., Grela, K. *Chem. Commun.* **2006**, 841 ; Jansen, F.J.H.M., Lugtenburg, J. *Eur. J. Org. Chem.* **2000**, 829 ; Marfat, A., McGuirk, P.R., Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888 ; Savoia, D., Trombini, C., Umani-Ronchi, A. *J. Org. Chem.* **1978**, *43*, 2907.

²⁸⁵ Litt.: Balog, A., Geib, S.V., Curran, D.P. *J. Org. Chem.* **1995**, *60*, 345-352.

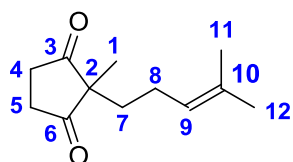
$R_f = 0.55$ (*n*-Pent/Et₂O, 75:25).

IR (neat): $\tilde{\nu} = 2924, 2866$ ($\nu_{\text{C-H alkyl}}$), 1667 ($\nu_{\text{C=C}}$), 1449 ($\delta_{\text{C-H alkyl}}$), 800 ($\delta_{\text{C-H vinyl}}$).

¹H NMR (CDCl₃, 300 MHz): δ 5.12-5.05 (m, 1H, H-5), 3.94-3.89 (m, 4H, H-9+ H-10), 2.04 (q, ³J₄₋₃ = ³J₄₋₅ = 8.1 Hz, 2H, H-4), 1.66 (s, 3H, H-8), 1.64-1.60 (m, 2H, H-3), 1.59 (s, 3H, H-7), 1.30 (s, 3H, H-1).

¹³C NMR (CDCl₃, 75 MHz): δ 131.4 (C-6), 124.1 (C-5), 109.9 (C-2), 64.6 (C-9 + C-10), 39.1 (C-3), 25.6 (C-4), 23.8 (C-1), 22.8 (C-7), 17.5 (C-8).

2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentane-1,3-dione **s13**²⁸⁶



C₁₂H₁₈O₂
194.3 g.mol⁻¹
Yellow oil
80%

Procedure A

To the acetal **s20** (121 mg, 0.710 mmol, 1.00 equiv.) dissolved in CH₂Cl₂ (3.6 mL, C = 0.2 M), BF₃·Et₂O (88 μ L, 0.71 mmol, 1.0 equiv.) and acyloin (0.29 mL, 95%, 1.1 mmol, 1.5 equiv.) were added at room temperature. The resulting mixture was then let stir for 2.7 h. After the completion of the reaction was monitored by TLC (*n*-Pent/Et₂O, 70:30), the reaction was quenched with distilled water (5 mL). The aqueous layer was extracted with Et₂O (3 x 5 mL), and the combined organic extracts were washed with brine (1 x 5 mL), dried over MgSO₄ and filtered. Solvent evaporation under reduced pressure gave crude dione, which was purified by flash chromatography on silica gel (*n*-Pent/Et₂O, 70:30). A yellow oil was obtained as the pure product (17 mg, 0.087 mmol, 12%).

Procedure B

The substrate **s23** (14.6 g, 88.0 mmol, 1 equiv.) was dissolved into 2-methyl-2-butene (94 mL, 88.0 mmol, 10 equiv.). A yellow solution was obtained, to which Grubbs II catalyst (374 mg, 0.440 mmol, 0.5 mol%) was added at room temperature, before the reaction mixture was heated to 40°C overnight. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 7:3). The reaction mixture was then filtered through a short pad of silica, and concentrated under reduced pressure to afford a brown oil as a crude product. The latter was purified by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9:1) to give a yellow oil as a pure product (13.7 g, 70.6 mmol, 80%).

$R_f = 0.44$ (*n*-Pent/EtOAc, 70:30).

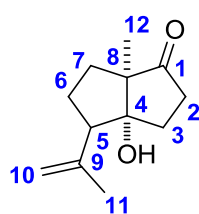
²⁸⁶ Litt.: Balog, A., Geib, S.J., Curran, D.P. *J. Org. Chem.* **1995**, *60*, 345.

IR (neat): $\tilde{\nu}$ = 2922, 2858 ($\nu_{\text{C-H alkyl}}$), 1722 ($\nu_{\text{C=O}}$), 1454 ($\delta_{\text{C-H alkyl}}$), 838 ($\delta_{\text{C-H vinyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 4.95-4.89 (m, 1H, H-9), 2.81-2.61 (m, 4H, H-4 + H-5), 1.93-1.81 (m, 2H, H-7), 1.76-1.73 (m, 2H, H-8), 1.62 (s, 3H, H-12), 1.52 (s, 3H, H-11), 1.10 (s, 3H, H-1).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 216.8 (C-3 + C-6), 133.2 (C-10), 123.4 (C-9), 56.5 (C-2), 35.7 (C-7), 35.2 (C-4 + C-5), 25.6 (C-11), 23.6 (C-8), 20.2 (C-1), 17.7 (C-12).

3 α -hydroxy-6 α -methyl-4-(prop-1-en-2-yl)hexahydropentalen-1(2H)-one s27



R_f = 0.54 (*n*-Pent/Et₂O, 8.5:1.5).

IR (neat): $\tilde{\nu}$ = 3476 (ν_{OH}), 2955, 2924, 2855 ($\nu_{\text{C-H alkyl}}$), 1737 ($\nu_{\text{C=O}}$), 1639 ($\nu_{\text{C=C}}$), 1460, 1375 ($\delta_{\text{C-H alkyl}}$), 1261 ($\nu_{\text{C-O}}$), 1031 (δ_{OH}), 891 ($\delta_{\text{C-H vinyl}}$).

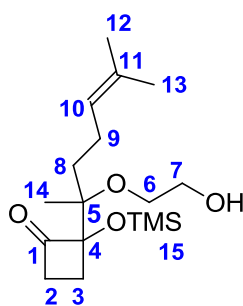
$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 5.07 (1 H, s, H-10), 4.87 (1 H, s, H-10), 2.56-2.19 (4 H, m, H-2 + H-5 + H-7), 2.00-1.81 (3 H, m, H-3 + H-6 + H-7), 1.87 (3 H, s, H-11) 1.75-1.41 (2 H, m, H-3 + H-6), 1.06 (3 H, s, H-12).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 221.9 (C-1), 143.8 (C-9), 114.0 (C-10), 86.2 (C-8), 59.9 (C-4), 54.6 (C-5), 35.5 (C-2), 33.4 (C-3), 30.6 (C-7), 28.2 (C-6), 24.5 (C-11), 17.1 (C-12).

MS (ES⁺): *m/z* (rel. intensity): 217 (100), 218 (10).

HRMS (ES⁺) calcd for $[(\text{C}_{12}\text{H}_{18}\text{O}_2 + \text{Na})^+]$: 217.11990; found: 217.11979.

2-(2-(2-hydroxyethoxy)-6-methylhept-5-en-2-yl)-2-((trimethylsilyl)oxy)cyclobuta-none s28



C₁₇H₃₂O₄Si
328,5 g.mol⁻¹

R_f = 0.62 (*n*-Pent/Et₂O, 1:1).

IR (neat): $\tilde{\nu}$ = 3417 (ν_{OH}), 2958, 2930, 2875 (ν_{C-H alkyl}), 1782 (ν_{C=O}), 1454, 1377 (δ_{C-H alkyl}), 1069 (δ_{OH}), 842 (δ_{C-H vinyl}).

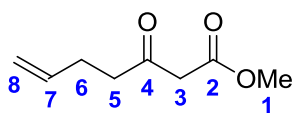
¹H NMR (CDCl₃, 300 MHz): δ 5.12-4.97 (m, 1H, H-10), 3.70-3.63 (m, 2H, H-2), 3.60-3.49 (m, 1H, H-3), 3.45-3.39 (m, 1H, H-3), 2.87-2.57 (m, 3H, H-6 + H-8), 2.18-1.77 (m, 3H, H-8 + H-9), 1.75-1.43 (m, 2H, H-7), 1.66 (s, 3H, H-12), 1.59 (s, 3H, H-13), 1.22 (s, 3H, H-14), 0.12 (s, 9H, H-15).

¹³C NMR (CDCl₃, 75 MHz): δ 213.8 (C-1), 131.4 (C-11), 124.6 (C-10), 97.3 (C-4), 79.5 (C-5), 63.8 (C-3), 62.5 (C-2), 42.2 (C-6), 34.8 (C-7), 25.8 (C-8), 25.4 (C-13), 22.9 (C-9), 18.2 (C-12), 17.7 (C-14), 1.5 (3 C-15).

MS (CI): *m/z* (rel. intensity): 351 (100), 352 (24), 353 (4).

HRMS (ES⁺) calcd for [(C₁₇H₃₂O₄Si + Na)⁺]: 351.19621; found: 351.19621.

Methyl-3-oxohept-6-enoate s33²⁸⁷



C₈H₁₂O₃
156.2 g.mol⁻¹
Yellow oil
76%

Methyl acetoacetate (0.94 mL, 99%, 8.6 mmol, 1.0 equiv.) was added very slowly to a suspension of NaH (517 mg, 60% disp. in oil, 12.9 mmol, 1.50 equiv.) in THF (14.0 mL) cooled at 0°C. At this temperature, the mixture was stirred for 10 min and *n*-BuLi (4.1 mL, 2.3 M, 9.5 mmol, 1.1 equiv.) was slowly added. At the same temperature, the mixture was stirred for additional 10 min and 1-

bromo-3-methyl-2-butene (1.2 mL, 90%, 9.5 mmol, 1.1 equiv.) was quickly added. After additional 5 min stirring at 0°C, the completion of the reaction was monitored by TLC (*n*-Pent/Et₂O, 90/10). The mixture was quenched by the careful addition of 1 M HCl (20 mL) and extracted with Et₂O (3 x 10 mL), and the combined organic extracts were washed with saturated NaHCO₃ (1 x 15 mL) solution and brine (1 x 15 mL). The resulting organic layer was dried over MgSO₄, filtered and concentrated under vacuum. Pure methyl-7-methyl-3-oxooct-6-enoate was isolated as a yellow oil (1.20 g, 6.50 mmol, 76%) by flash chromatography on silica gel (*n*-Pent/Et₂O, 90:10). A mixture of ketone and enol tautomers in a 10:1 ratio was obtained.

R_f = 0.29 (*n*-Pent/Et₂O, 85:15).

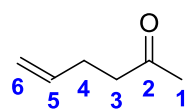
²⁸⁷ Litt.: Hiebel, M.-A., Pelotier, B., Goekjian, P., Piva, O. *Eur. J. Org. Chem.* **2008**, 713.

IR (neat): $\tilde{\nu}$ = 3080, 2955 ($\nu_{\text{C-H alkyl}}$), 1743, 1715 ($\nu_{\text{C=O}}$), 1642 ($\nu_{\text{C=C}}$), 1437 ($\delta_{\text{C-H alkyl}}$), 1408, 998, 914 ($\delta_{\text{C-H vinyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 5.79 (ddt, $^3J_{7-6} = 6.8$ Hz, $^3J_{\text{cis } 7-8} = 10.3$ Hz, $^3J_{\text{trans } 7-8} = 17.0$ Hz, 1H, H-7), 5.08-4.95 (m, 2H, H-8), 3.73 (s, 3H, H-1), 3.45 (s, 2H, H-3), 2.64 (t, $^3J_{5-6} = 6.8$ Hz, 2H, H-5), 2.34 (q, $^3J_{6-5} = ^3J_{6-7} = 6.8$ Hz, 2H, H-6).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 208.5 (C-4), 167.8 (C-2), 137.2 (C-7), 115.4 (C-8), 53.6 (C-3), 42.9 (C-5), 30.1 (C-1), 27.8 (C-6).

Hex-5-en-2-one **s34**²⁸⁸



$\text{C}_6\text{H}_{10}\text{O}$
98.1 $\text{g}\cdot\text{mol}^{-1}$
Light orange oil
19%

Crude methyl 3-oxohept-6-enoate **s33** (237 mg, 1.52 mmol) was dissolved into a 10% sodium hydroxide aqueous solution (7.0 mL, $\geq 97.5\%$) and refluxed for 21.5 h. After the completion of the reaction was monitored by TLC (*n*-Pent/ Et_2O , 1:1), the mixture was let return to room temperature for 30 min. Then, the mixture was quenched by the careful addition of 6 M HCl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried over MgSO_4 , filtered and concentrated under vacuum. Crude hex-5-en-2-one was obtained as a light orange oil (28 mg, 0.29 mmol, 19%).

$R_f = 0.31$ (*n*-Pent/ Et_2O , 9:1).

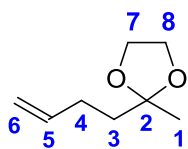
IR (neat): $\tilde{\nu}$ = 3077, 2925 ($\nu_{\text{C-H alkyl}}$), 1714 ($\nu_{\text{C=O}}$), 1669 ($\nu_{\text{C=C}}$), 1442 ($\delta_{\text{C-H alkyl}}$), 1407, 995, 913 ($\delta_{\text{C-H vinyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 5.80 (ddt, $^3J_{5-4} = 6.8$ Hz, $^3J_{\text{cis } 5-6} = 10.3$ Hz, $^3J_{\text{trans } 5-6} = 17.0$ Hz, 1H, H-5), 5.08-4.94 (m, 2H, H-6), 2.53 (t, $^3J_{3-4} = 6.8$ Hz, 2H, H-3), 2.32 (q, $^3J_{4-3} = ^3J_{4-5} = 6.8$ Hz, 2H, H-4); 2.14 (s, 3H, H-1).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 208.0 (C-2), 137.0 (C-5), 115.2 (C-6), 42.7 (C-3), 29.9 (C-1), 27.8 (C-4).

2-(but-3-en-1-yl)-2-methyl-1,3-dioxolane **s19**²⁸⁹

²⁸⁸ Litt.: Lin, K.-W., Hsieh, I.-L., Tsai, C.-H., Yan, T.-H. *Org. Lett.* **2008**, *10*, 1927.



$C_8H_{14}O_2$
 142.2 $g \cdot mol^{-1}$
 Colorless oil
 65%

Hex-5-en-2-one **s34** (21.3 mL, 182 mmol, 1.00 equiv.) was added neat to a solution of ethylene glycol (71.2 mL, 99.8%, 1.30 mol, 7.00 equiv.) and trimethyl orthoformate (60.3 mL, 99%, 546 mmol, 3.00 equiv.), followed by the addition of *p*-toluenesulfonic acid (4.7 g, 99.5%, 27 mmol, 15 mol%). After 5 h, the completion of the reaction was monitored by TLC (*n*-Pent/ Et_2O , 75:25) and the mixture was quenched with saturated $NaHCO_3$ solution (150 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic extracts were washed with distilled water (2 x 100 mL) and brine (1 x 100 mL). The resulting organic layer was dried over $MgSO_4$, filtered and solvent evaporation under reduced pressure gave crude acetal, which was purified by flash chromatography on silica gel (*n*-Pent/ Et_2O , 9:1) to afford a colorless oil (16.8 g, 118 mmol, 65%) as the pure product.

$R_f = 0.53$ (*n*-Pent/ Et_2O , 7.5:2.5).

IR (neat): $\tilde{\nu} = 3078, 2982, 2948, 2879$ ($\nu_{C-H \text{ alkyl}}$), 1642 ($\nu_{C=C}$), 1478, 1452, 1407 ($\delta_{C-H \text{ vinyl}}$), 1376 ($\delta_{C-H \text{ alkyl}}$), 996, 909 ($\delta_{C-H \text{ vinyl}}$).

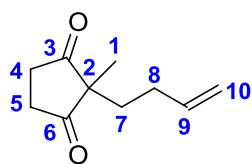
1H NMR ($CDCl_3$, 300 MHz): $\delta = 5.83$ (ddt, $^3J_{5-4} = 6.6$ Hz, $^3J_{cis \ 5-6} = 10.3$ Hz, $^3J_{trans \ 5-6} = 17.1$ Hz, 1H, H-5), 5.07-4.98 (m, 1H, H-6), 4.97-4.89 (m, 1H, H-6), 4.00-3.88 (m, 4H, H-7 + H-8), 2.21-2.10 (m, 2H, H-4), 1.78-1.69 (m, 2H, H-3), 1.33 (s, 3H, H-1).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.5 (C-5), 114.2 (C-6), 109.8 (C-2), 64.7 (C-7 + C-8), 38.3 (C-3), 28.3 (C-4), 23.9 (C-1).

2-(but-3-en-1-yl)-2-methylcyclopentane-1,3-dione **s23**²⁹⁰

²⁸⁹ Litt.: Elliot, C.E., Miller, D.O., Burnell, D.J. *J. Chem. Soc., Perkin Trans. I* **2002**, 217; Backes, J.R., Koert, U. *Eur. J. Org. Chem.* **2006**, 2777.

²⁹⁰ Litt.: Balog, A., Geib, S.J., Curran, D.P. *J. Org. Chem.* **1995**, 60, 345; Elliot, C.E., Miller, D.O., Burnell, D.J. *J. Chem. Soc., Perkin Trans. I* **2002**, 217.



$C_{10}H_{14}O_2$
 166.2 g.mol⁻¹
 Colorless oil
 73%

To the acetal **s19** (2.5 g, 17.6 mmol, 1.00 equiv.) dissolved in CH_2Cl_2 (176 mL, C = 0.1 M) and cooled at $-78^\circ C$, $BF_3 \cdot Et_2O$ (21.7 mL, 176 mmol, 10 equiv.) was added dropwise. After 10 min at this temperature, succinoin (6.2 mL, 95%, 22.9 mmol, 1.3 equiv.) was slowly added. After 3 h stirring of the resulting mixture at $-78^\circ C$, the latter was placed at $5^\circ C$ for ten minutes. The completion of the reaction was monitored by TLC (*n*-Pent/ Et_2O , 70:30) and the mixture was quenched with distilled water (200 mL). The aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organic extracts were washed with brine (1 x 200 mL). The resulting organic layer was dried over $MgSO_4$, filtered and evaporation of the solvent at room temperature under reduced pressure gave crude dione, which was purified by flash chromatography on silica gel (*n*-Pent/ Et_2O , 7.5:2.5) to afford a colorless oil (2.12 g, 12.8 mmol, 73%) as the pure product.

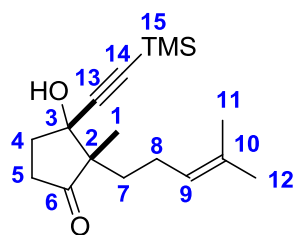
$R_f = 0.20$ (*n*-Pent/ Et_2O , 7.5:2.5).

IR (neat): $\tilde{\nu} = 3078, 2923, 2854$ (ν_{C-H} alkyl), 1764, 1718 ($\nu_{C=O}$), 1642 ($\nu_{C=C}$), 1452, 1420 (δ_{C-H} vinyl), 1373 (δ_{C-H} alkyl), 993, 914 (δ_{C-H} vinyl).

1H NMR ($CDCl_3$, 300 MHz): δ 5.60 (ddt, $^3J_{9-8} = 6.7$ Hz, $^3J_{cis-9-10} = 10.2$ Hz, $^3J_{trans-9-10} = 17.0$ Hz, 1H, H-9), 4.98-4.83 (m, 2H, H-10), 2.84-2.60 (m, 4H, H-4 + H-5), 1.98-1.84 (m, 2H, H-7), 1.79-1.66 (m, 2H, H-8), 1.07 (s, 3H, H-1).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 216.6 (C-3 + C-6), 137.4 (C-9), 115.9 (C-10), 56, 3 (C-2), 35.2 (C-4 + C-5), 34.2 (C-7), 29.2 (C-8), 20.2 (C-1).

3-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-3-((trimethylsilyl)ethynyl)cyclopentanone **s35**



$C_{17}H_{28}O_2Si$
 292.5 g.mol⁻¹
 Orange powder
 81%

THF (16.0 mL) was added to anhydrous $CeCl_3$ (2.2 g, 8.9 mmol, 3.5 equiv.) and the resulting suspension was stirred at room temperature for 2 h. In another flask, to a solution of trimethylsilylacetylene (1.2 mL, 8.4 mmol, 3.3 equiv.) in THF (16.0 mL) cooled at $-78^\circ C$, *n*-BuLi (3.3 mL, 2.3 M, 7.7 mmol, 3.0 equiv.) was added dropwise. The resulting mixture was stirred at this temperature for 30 min to give a solution of 2-trimethylsilylethynyllithium, which was then cannulated to the prepared suspension of $CeCl_3$ in THF cooled at $-78^\circ C$. After the stirring

was continued at the same temperature for additional 30 min, the diketone **13** (495 mg, 2.55 mmol, 1.00 equiv.) was introduced as a solution in THF (4 mL). After 3 h at the same temperature, the completion of the reaction was monitored by TLC (*n*-Pent/ Et_2O , 7.5:2.5). The mixture was quenched at room temperature with distilled water (40 mL). The aqueous layer was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a brown oil as the crude product, which was purified by flash chromatography on silica gel (*n*-Pent/ Et_2O , 85/15). Pure TMS-protected alkyne was isolated as an orange powder (603 mg, 2.07 mmol, 81%).

$R_f = 0.28$ (PE/ $EtOAc$, 7:3).

Mp = $70.5^\circ C$.

IR (neat): $\tilde{\nu} = 3433$ (ν_{OH}), 2962, 2925, 2857 (ν_{C-H} alkyl), 2164 ($\nu_{C\equiv C}$), 1731 ($\nu_{C=O}$), 1459, 1373 (δ_{C-H} alkyl), 839 (δ_{C-H} vinyl).

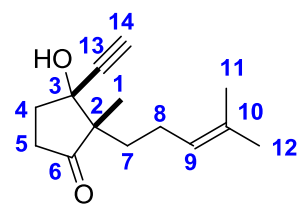
1H NMR ($CDCl_3$, 300 MHz): δ 5.21-5.08 (1 H, m, H-9), 2.37-2.10 (7 H, m, H-4 + H-5 + H-7 + OH), 1.65 (3 H, s, H-12), 1.59-1.53 (2 H, m, H-8), 1.61 (3 H, s, H-11), 1.10 (3 H, s, H-1), 0.15 (9 H, s, H-15).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 219.2 (C-6), 131.9 (C-10), 124.8 (C-9), 106.4 (C-13), 91.8 (C-14), 76.7 (C-3), 56.3 (C-2), 34.9 (C-4), 33.5 (C-5), 30.9 (C-7), 25.7 (C-11), 22.4 (C-8), 19.0 (C-1), 17.8 (C-12), 0.12 (9 H, s, 3 C-15).

MS (CI): *m/z* (rel. intensity): 315 (100), 316 (24), 317 (3).

HRMS (CI) calcd for $[(C_{17}H_{28}O_2Si + Na)]^+$: 315.17508; **found**: 315.17501.

3-ethynyl-3-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentanone **s36**



$C_{14}H_{20}O_2$
220.3 g.mol⁻¹
Pale yellow powder
81%

To the TMS-protected alkyne **s35** (4.2 g, 14 mmol, 1.0 equiv.) dissolved in MeOH (14.4 mL) was added K_2CO_3 (4.0 mg, 29 mmol, 2.0 equiv.). The heterogeneous mixture was stirred at room temperature for 18 h under argon atmosphere. After the completion of the reaction was monitored by TLC (PE/Et₂O, 7:3), the reaction mixture was diluted with EtOAc (15 mL), and washed with distilled water (1 x 10 mL) and brine (2 x 10 mL). The resulting organic layer was dried over Na_2SO_4 , filtered and concentrated under vacuum. Purification by flash chromatography on silica gel (PE/Et₂O, 7:3) then afforded pure deprotected alkyne as a pale yellow powder (2.6 mg, 12 mmol, 81%).

R_f = 0.21 (Pent/EtOAc, 8.5:1.5).

Mp = 75.0°C.

IR (neat): $\tilde{\nu}$ = 3435, 3294 (ν_{OH}), 2966, 2924, 2857 (ν_{C-H} alkyl), 1975 ($\nu_{C=C}$), 1733 ($\nu_{C=O}$), 1459, 1374 (δ_{C-H} alkyl), 1271 (ν_{C-O}), 1107 (δ_{OH}), 835, 798 (δ_{C-H} vinyl), 651 (δ_{C-H} alkynyl).

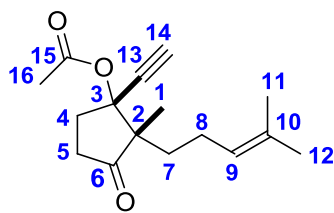
¹H NMR (CDCl₃, 400 MHz): δ 5.14 (1 H, m, H-**9**), 2.64 (1 H, s, H-**14**), 2.55-2.18 (7 H, m, H-**4** + H-**5** + H-**7** + OH), 1.68 (3 H, s, H-**12**), 1.65-1.55 (2 H, m, H-**8**), 1.62 (3 H, s, H-**11**), 1.14 (3 H, s, H-**1**).

¹³C NMR (CDCl₃, 100 MHz): δ 218.8 (C-**6**), 132.3 (C-**10**), 124.6 (C-**9**), 84.6 (C-**13**), 76.6 (C-**3**), 75.4 (C-**14**), 56.3 (C-**2**), 35.1 (C-**4**), 33.5 (C-**5**), 31.0 (C-**7**), 25.8 (C-**11**), 22.5 (C-**8**), 19.0 (C-**1**), 17.8 (C-**12**).

MS (CI): m/z (rel. intensity): 243 (100), 244 (14).

HRMS (CI) calcd for $[(C_{14}H_{20}O_2 + Na)^+]$: 243.13555; **found**: 243.13570.

1-ethynyl-2-methyl-2-(4-methylpent-3-en-1-yl)-3-oxocyclopentyl acetate **s37**



C₁₆H₂₂O₃
262.3 g.mol⁻¹
Pale yellow powder
98%

To a solution of the deprotected alkyne **s36** (2.6 g, 12 mmol, 1.00 equiv.) and DMAP (966 mg, 99%, 7.80 mmol, 68.0 mol%) in CH₂Cl₂ (19.0 mL), Et₃N (4.9 mL, 35 mmol, 3.0 equiv.) and acetic anhydride (4.4 mL, 99%, 46 mmol, 4.0 equiv.) were added. The resulting mixture was stirred for 18.8 h at reflux (T^b_{CH₂Cl₂} = 40°C). The completion of the reaction was monitored by TLC (PE/Et₂O, 1:1) and the mixture was quenched at room temperature with distilled water (25 mL). The aqueous layer was

extracted with CH₂Cl₂ (4 x 10 mL) and the combined organic extracts were washed with brine (2 x 20 mL), dried over Na₂SO₄ and filtered. The solvent was evaporated under reduced pressure, affording a crude residue which was purified by flash chromatography on silica gel (*n*-Pent/Et₂O, 2:1). Pure acetate was obtained as a pale yellow powder (3.0 g, 12 mmol, 98%).

R_f = 0.47 (PE/Et₂O, 1:1).

Mp = 80.2°C.

IR (neat): $\tilde{\nu}$ = 2962, 2925, 2855 (ν_{C-H alkyl}), 2117 (ν_{C≡C}), 1735 (ν_{C=O}), 1454, 1371 (δ_{C-H alkyl}), 1307 (ν_{C-O}), 832 (δ_{C-H vinyl}), 609 (δ_{C-H alkyne}).

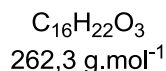
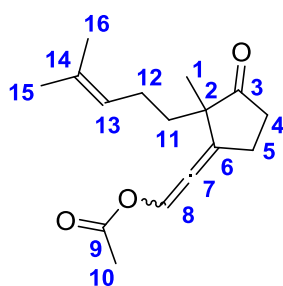
¹H NMR (CDCl₃, 400 MHz): δ 5.13-5.06 (1 H, m, H-9), 2.90-2.80 (1 H, m, H-4), 2.75 (1 H, s, H-14), 2.54-2.26 (3 H, m, H-4 + H-5), 2.23-2.01 (2 H, m, H-7), 2.06 (3 H, s, H-16), 1.68 (3 H, s, H-12), 1.65-1.54 (2 H, m, H-8), 1.60 (3 H, s, H-11), 1.22 (3 H, s, H-1).

¹³C NMR (CDCl₃, 100 MHz): δ 216.6 (C-6), 169.1 (C-15), 132.1 (C-10), 124.3 (C-9), 82.4 (C-13), 80.5 (C-14), 78.0 (C-3), 56.7 (C-2), 33.4 (C-5), 31.6 (C-4), 30.7 (C-8), 25.7 (C-11), 22.6 (C-7), 21.7 (C-16), 18.3 (C-1), 17.7 (C-12).

MS (CI): *m/z* (rel. intensity): 285 (100), 286 (17), 288 (5).

HRMS (CI) calcd for ([C₁₄H₂₀O₂ + Na]⁺): 285.14612; found: 285.14669.

2-(2-methyl-2-(4-methylpent-3-en-1-yl)-3-oxocyclopentylidene)vinyl acetate **s40**



The catalyst was added to a solution of the acetate **s37** in anhydrous CH_2Cl_2 or toluene ($C = 0.025 \text{ mol.L}^{-1}$). The reaction was run at room temperature with Echavarren's catalyst (99%, 2 mol%). Its completion was monitored by TLC (PE/Et₂O, 1:1). When the reaction was complete, the mixture was filtered through a short pad of silica in a glass frit. The solvent was then removed under vacuum, and purification by flash chromatography (*n*-Pent/Et₂O, 9:1) afforded the cycloisomerization products.

$R_f = 0.56$ (PE/Et₂O, 1:1)

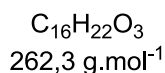
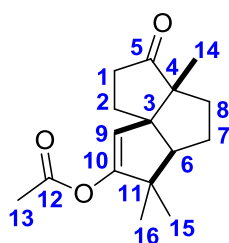
IR (neat): $\tilde{\nu} = 2966, 2925, 2857$ ($\nu_{C-H \text{ alkyl}}$), 1980 ($\nu_{C=C \text{ allene}}$), 1743 ($\nu_{C=O}$), 1450 ($\delta_{C-H \text{ alkyl}}$), 1409 (ν_{C-O}), 1369 ($\delta_{C-H \text{ alkyl}}$), 1293 (ν_{C-O}), $948, 796$ ($\delta_{C-H \text{ vinyl}}$).

¹H NMR (CDCl₃, 400 MHz): δ 7.56-7.49 (1 H, m, H-**8**), 5.06-4.93 (1 H, m, H-**13**), 2.81-2.70 (2 H, m, H-**5**), 2.49-2.36 (2 H, m, H-**4**), 2.11 (3 H, s, H-**10**), 2.05-1.72 (2 H, m, H-**12**), 1.63 (3 H, s, H-**15**), 1.68-1.38 (2 H, s, H-**11**), 1.56 (3 H, m, H-**16**), 1.09 (3 H, s, H-**1**).

¹³C NMR (CDCl₃, 100 MHz): δ 219.3 (C-**3**), 187.0 (C-**7**), 168.5 (C-**9**), 132.2 (C-**14**), 125.7 (C-**13**), 122.6 (C-**6**), 113.3 (C-**8**), 53.3 (C-**2**), 37.6 (C-**11**), 36.5 (C-**4**), 25.7 (C-**5**), 25.6 (C-**15**), 23.4 (C-**12**), 22.8 (C-**1**), 20.9 (C-**10**), 17.7 (C-**16**).

HRMS (ES+) calcd for $[(C_{16}H_{22}O_3 + Na)^+]$: 285.14612; **found**: 285.14650.

3,3,5a-trimethyl-6-oxo-3,3a,4,5,5a,6,7,8-octahydrocyclopenta[c]pentalen-2-yl acetate **s42**



IR (neat): $\tilde{\nu} = 2957, 2868$ ($\nu_{C-H \text{ alkyl}}$), $1754, 1736$ ($\nu_{C=O}$), 1651 ($\nu_{C=C}$), $1458, 1369$ ($\delta_{C-H \text{ alkyl}}$), $1346, 1308$ (ν_{C-O}), 831 ($\delta_{C-H \text{ vinyl}}$).

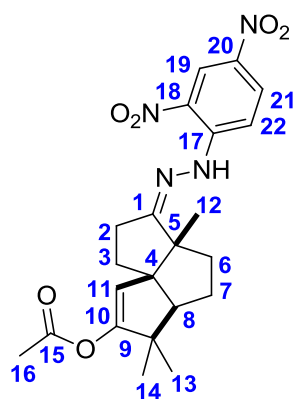
¹H NMR (CDCl₃, 400 MHz): δ 5.33 (s, 1H H-**9**), 2.41-2.22 (m, 2H, H-**1**), 2.22-1.83 (m, 3H, H-**6**+H-**7**+H-**2**), 2.13 (s, 3H, H-**13**), 1.70-1.54 (m, 1H, H-**8**), 1.46-1.26 (m, 2H, H-**1**+H-**8**), 1.12 (s, 3H, H-**14**), 0.95 (s, 3H, H-**15** or H-**16**), 0.91 (s, 3H, H-**15** or H-**16**).

¹³C NMR (CDCl₃, 100 MHz): δ 224.8 (C-**5**), 168.3 (C-**12**), 156.0 (C-**9**), 113.1 (C-**10**), 63.2 (C-**11**), 58.8 (C-**3**), 57.8 (C-**6**), 46.1 (C-**4**), 38.2 (C-**7**), 37.1 (C-**1**), 32.4 (C-**2**), 31.3 (C-**14**), 27.7 (C-**8**), 21.6 (C-**15** or C-**16**), 21.3 (C-**13**), 17.5 (C-**15** or C-**16**).

HRMS (ES+) calcd for $[(C_{16}H_{22}O_3 + Na)^+]$: 285.1461; found: 285.1469.

3,3,5a-trimethyl-6-(2-(4-nitrophenyl)hydrazono)-3,3a,4,5,5a,6,7,8-

octahydrocyclopenta[c]pentalen-2-yl acetate **s47**



$C_{22}H_{27}N_3O_4$
397,5 g.mol⁻¹
Orange crystals
99%

The starting material **s42** (66 mg, 0.252 mmol, 1 equiv.) and 2, 4-dinitrophenylhydrazine (75 mg, 0.378 mmol, 1.5 equiv.) were dissolved in toluene (4.5 mL). An orange solution was obtained, to which PTSA (2 mg, 0.0126 mmol, 5 mol%) was added. The reaction mixture was heated to reflux for 3 h. The completion of the reaction was monitored by TLC (PE/Et₂O, 1:1). The reaction mixture was concentrated under vacuum to yield a red-orange powder that was purified by flash column chromatography on silica gel (*n*-Pent/Et₂O, 9.2:0.8). The pure compound was obtained as orange crystals (111 mg, 0.279 mmol, 99%).

Mp : degrades at T > 150°C.

$R_f = 0.16$ (PE/Et₂O, 9:1).

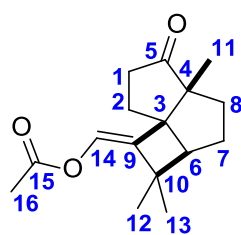
IR (neat): $\tilde{\nu} = 3318$ (ν_{N-H} sec), 2956, 2928, 2867 (ν_{C-H} alkyl), 1753 ($\nu_{C=O}$), 1650 ($\nu_{C=C}$), 1617 ($\nu_{C=N}$), 1591 ($\nu_{C=C}$ Ar), 1517 (ν_{C-NO_2} Ar), 1504, 1457 ($\nu_{C=C}$ Ar), 1423 (ν_{C-H} alkyl), 1362, 1334, 1310 (ν_{C-NO_2} Ar), 1283 (ν_{C-O}), 889, 832 (δ_{C-H} Ar).

¹H NMR (CDCl₃, 400 MHz): δ 10.8 (s, 1H, NH), 9.10 (d, $J = 2.6$ Hz, 1H, H-**19**), 8.27 (dd, $J = 9.6, 2.5$ Hz, 1H, H-**21**), 7.96 (d, $J = 9.6$ Hz, 1H, H-**22**), 5.35 (s, 1H, H-**11**), 2.73 (ddd, $J = 17.8, 7.0, 3.2$ Hz, 1H, CH₂₁), 2.53-2.39 (m, 1H, CH₂₁), 2.18 (s, 3H, H-**16**), 2.11-1.95 (m, 4H, CH₂₂ + CH₂₃ + H-**8**), 1.74-1.50 (m, 2H, CH₂₃ + CH₂₄), 1.50-1.35 (m, 1H, CH₂₄), 1.16 (s, 3H, H-**13** or H-**14**), 1.15 (s, 3H, H-**13** or H-**14**), 1.01 (s, 3H, H-**12**).

¹³C NMR (CDCl₃, 100 MHz): δ 173.2 (C-**1**), 168.6 (C-**15**), 155.0 (C-**10**), 145.2 (C-**20**), 137.7 (C-**18**), 130.0 (C-**21**), 129.0 (C-**17**), 123.6 (C-**19**), 116.5 (C-**22**), 112.3 (C-**11**), 65.1 (C-**5**), 57.1 (C-**9**), 56.9 (C-**8**), 46.3 (C-**4**), 40.1, 34.5 (CH₂) 31.5 (C-**13** or C-**14**), 27.4, 27.3 (CH₂), 21.8 (C-**12**), 21.4 (C-**16**), 21.2 (C-**13** or C-**14**).

HRMS (ES+) calcd for $[(C_{22}H_{26}N_4O_6 + Na)^+]$: 465.1745; found: 465.1757.

(E)-(2,2,4a-trimethyl-5-oxooctahydro-1H-cyclobuta[c]pentalen-1-ylidene)methyl acetate s41



$C_{16}H_{22}O_3$
262,3 g.mol⁻¹

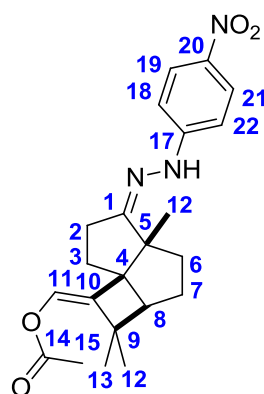
IR (neat): $\tilde{\nu}$ = 2954, 2928, 2864 (ν_{C-H} alkyl), 1753, 1737 ($\nu_{C=O}$), 1693 ($\nu_{C=C}$), 1459, 1370 (δ_{C-H} alkyl), 1290, 1270 (ν_{C-O}), 827 (δ_{C-H} vinyl).

¹H NMR (CDCl₃, 400 MHz): δ 6.85 (s, 1H, H-14), 2.43-2.29 (m, 1H, H-1), 2.28-2.02 (m, 4H, H-7+H-1+H-8+H-6), 2.10 (s, 3H, H-16), 1.99-1.89 (m, 1H, H-8), 1.65-1.46 (m, 2H, H-7+H-2), 1.38-1.24 (m, 1H, H-2), 1.29 (s, 3H, H-12 or H-13), 1.07 (s, 3H, H-12 or H-13), 0.92 (s, 3H, H-11).

¹³C NMR (CDCl₃, 100 MHz): δ 223.7 (C-5), 167.8 (C-15), 135.8 (C-9), 129.2 (C-14), 59.3 (C-4), 57.9 (C-3), 55.0 (C-6), 38.9 (C-10), 38.7 (C-7), 36.3 (C-1), 30.4 (C-8), 29.8 (C-12 or C-13), 26.3 (C-2), 20.8 (C-16), 19.8 (C-12 or C-13), 16.9 (C-11).

HRMS (ES+) calcd for ([C₁₆H₂₂O₃ + Na]⁺): 285.14612; **found**: 285.14647.

(E)-(2,2,4a-trimethyl-5-(2-(4-nitrophenyl)hydrazono)octahydro-1H-cyclobuta[c]pentalen-1-ylidene)methyl acetate s46



$C_{22}H_{27}N_3O_4$
397,5 g.mol⁻¹
Orange crystals
39%

The starting material **s41** (29 mg, 0.111 mmol, 1 equiv.) and 2, 4-dinitrophenylhydrazine (150 mg, 0.756 mmol, 3 equiv.) were dissolved in toluene (4.5 mL). An orange solution was obtained, to which PTSA (4 mg, 0.0222 mmol, 20 mol%) was added. The reaction mixture was heated to reflux for 3 h. The completion of the reaction was monitored by TLC (PE/Et₂O, 7:3). The reaction mixture was concentrated under vacuum to yield a red-orange powder that was purified by flash column chromatography on silica gel (*n*-Pent/Et₂O, 7.5:2.5). The pure compound was obtained as orange crystals (17 mg, 0.0428 mmol, 39%).

Mp = 165°C.

R_f = 0.30 (*n*-Pent/Et₂O, 7.5:2.5).

IR (neat): $\tilde{\nu}$ = 3317 (ν_{N-H} sec), 2956, 2929, 2864 (ν_{C-H} alkyl), 1752 ($\nu_{C=O}$), 1693 ($\nu_{C=C}$), 1617 ($\nu_{C=N}$), 1591 ($\nu_{C=C}$ Ar), 1537, 1517 (ν_{C-NO_2} Ar), 1504, 1457 ($\nu_{C=C}$ Ar), 1424 (ν_{C-H} alkyl), 1362, 1335, 1311 (ν_{C-NO_2} Ar), 1282 (ν_{C-O}), 884, 833 (δ_{C-H} Ar).

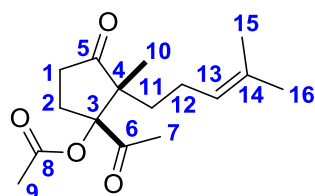
$^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 10.80 (s, 1H, NH), 9.11 (d, $J = 2.5$ Hz, 1H, H-19), 8.29 (ddd, $J = 9.6$, 2.6, 0.8 Hz, 1H, H-21), 7.96 (d, $J = 9.6$ Hz, 1H, H-22), 6.91 (s, 1H, H-11), 2.69 (dd, $J = 17.5$, 9.4 Hz, 1H, H-2 or H-3), 2.51-2.29 (m, 3H, H-2 + H-3 + H-6), 2.15 (s, 3H, H-16), 2.11-1.98 (m, 2H, H-2 or H-3 + H-8), 1.79 (td, $J = 12.8$, 7.1 Hz, 1H, H-6), 1.68 (dd, $J = 13.9$, 7.1 Hz, 1H, H-7), 1.53-1.39 (m, 1H, H-7), 1.34 (s, 3H, H-13 or H-14), 1.16 (s, 3H, H-12), 1.14 (s, 3H, H-13 or H-14).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 171.7 (C-1), 167.9 (C-15), 145.2 (C-20), 137.8 (C-18), 135.2 (C-10), 130.1 (C-21), 129.4 (C-11), 129.1 (C-17), 123.7 (C-19), 110.5 (C-22), 59.6 (C-4), 56.8 (C-5), 54.5 (C-8), 40.5 (C-6), 38.7 (C-9), 32.5 (C-2 or C-3), 29.8 (C-13 or C-14), 26.3 (C-2 or C-3), 26.2 (C-7), 20.9 (C-16), 20.7 (C-12), 19.9 (C-13 or C-14).

HRMS (ES+) calcd for $[(\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_6 + \text{Na})^+]$: 441.1780; found: 441.1766.

1-acetyl-2-methyl-2-(4-methylpent-3-en-1-yl)-3-oxocyclopentyl

acetate **s57**



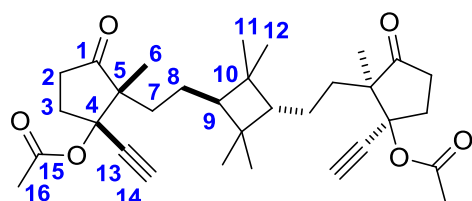
IR (neat): $\tilde{\nu} = 2968$, 2929 ($\nu_{\text{C-H alkyl}}$), 1739, 1714 ($\nu_{\text{C=O}}$), 1666 ($\nu_{\text{C=C}}$), 1454 ($\delta_{\text{C-H alkyl}}$), 1407 ($\nu_{\text{C-O}}$), 1370 ($\delta_{\text{C-H alkyl}}$), 834 ($\delta_{\text{C-H vinyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 5.10-5.00 (m, 1H, H-13), 2.88 (ddd, 1H, H-2), 2.58-2.35 (m, 2H, H-1), 2.23-2.07 (m, 1H, H-2), 2.16 (s, 3H, H-9), 2.12 (s, 3H, H-7), 2.06-1.92 (m, 2H, H-2+H-12), 1.70-1.54 (m, 2H, H-11+H-10), 1.68 (s, 3H, H-15 or H-16), 1.59 (s, 3H, H-15 or H-16), 0.97 (s, 3H, H-10).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 215.6 (C-5), 207.0 (C-6), 170.6 (C-8), 132.6 (C-14), 123.8 (C-13), 93.7 (C-3), 55.2 (C-4), 34.8 (C-1), 33.1 (C-11), 28.0 (C-2), 27.1 (C-7), 25.8 (C-15 or C-16), 22.7 (C-12), 21.3 (C-9), 17.8 (C-15 or C-16), 16.6 (C-10).

HRMS (ES+) calcd for $[(\text{C}_{16}\text{H}_{24}\text{O}_4 + \text{Na})^+]$: 303.1567; found: 303.1574.

((2,2,4,4-tetramethylcyclobutane-1,3-diyl)bis(ethane-2,1-diyl))bis(1-ethynyl-2-methyl-3-oxocyclopentane-2,1-diyl) diacetate **s56**



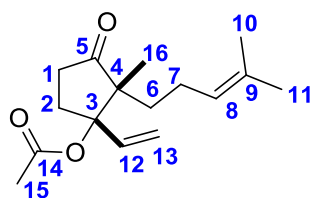
IR (neat): $\tilde{\nu} = 3269$ ($\nu_{\text{C-H alkynyl}}$), 2960, 2930, 2872 ($\nu_{\text{C-H alkyl}}$), 2106 ($\nu_{\text{C}\equiv\text{C}}$), 1731 ($\nu_{\text{C=O}}$), 1642 ($\nu_{\text{C=C}}$), 1454 ($\delta_{\text{C-H alkyl}}$), 1410 ($\nu_{\text{C-O}}$), 1367 ($\delta_{\text{C-H alkyl}}$), 629 ($\delta_{\text{C-H alkynyl}}$).

196 $\text{C}_{32}\text{H}_{44}\text{O}_6$
524,7 $\text{g}\cdot\text{mol}^{-1}$

$^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 2.54-2.30 (m, 4H, H-2 + H-3 + H-14), 2.29-2.09 (m, 2H, H-3 + H-9), 1.97 (s, 3H, H-16), 1.96-1.88 (m, 1H, H-7), 1.88-1.80 (m, 1H, H-8), 1.79-1.68 (m, 1H, H-8), 1.66 (s, 3H, H-11 or H-12), 1.65 (s, 3H, H-11 or H-12), 1.56 (ddd, $J = 12.4, 9.0, 3.2$ Hz, 1H, H-7), 1.16 (s, 3H, H-6).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 221.1 (C-1), 170.5 (C-15), 85.7 (C-13), 84.1 (C-10), 75.5 (C-14), 62.0 (C-5), 56.1 (C-9), 51.3 (C-4), 34.3 (C-2), 33.0 (C-3), 32.6 (C-7), 26.4 (C-8), 25.8 (C-11 or C-12), 24.4 (C-11 or C-12), 22.7 (C-16), 19.2 (C-6).

2-methyl-2-(4-methylpent-3-en-1-yl)-3-oxo-1-vinylcyclopentyl acetate **s38**



$\text{C}_{16}\text{H}_{24}\text{O}_3$
264,4 $\text{g}\cdot\text{mol}^{-1}$

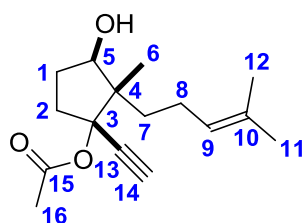
IR (neat): $\tilde{\nu} = 2965, 2921$ ($\nu_{\text{C-H alkyl}}$), 1739 ($\nu_{\text{C=O}}$), 1642 ($\nu_{\text{C=C}}$), 1461 ($\delta_{\text{C-H alkyl}}$), 1414 ($\delta_{\text{C-H vinyl}}$), 1369 ($\delta_{\text{C-H alkyl}}$), 833 ($\delta_{\text{C-H vinyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 5.88 (dd, $J = 17.6, 11.2$ Hz, 1H, H-12), 5.36-5.09 (m, 3H, H-8+H-13), 2.79-2.66 (m, 2H, H-1), 2.35-2.28 (m, 2H, H-2), 2.18-1.90 (m, 2H, H-7), 2.02 (s, 3H, H-15), 1.71-1.48 (m, 2H, H-6), 1.67 (s, 3H, H-11), 1.59 (s, 3H, H-10), 0.93 (s, 3H, H-16).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 218.8 (C-5), 169.6 (C-14), 136.1 (C-12), 131.9 (C-9), 124.5 (C-8), 91.4 (C-3), 56.2 (C-4), 33.7 (C-2), 31.6 (C-6), 26.5 (C-1), 25.8 (C-11), 22.9 (C-7), 22.0 (C-15), 17.7 (C-10), 17.6 (C-16).

HRMS (ES+) calcd for $([\text{C}_{16}\text{H}_{24}\text{O}_3 + \text{Na}]^+)$: 287.1618; **found**: 287.1611.

1-ethynyl-3-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentyl acetate **s58**



$\text{C}_{16}\text{H}_{24}\text{O}_3$
264.4 $\text{g}\cdot\text{mol}^{-1}$
White paste
57%

A solution (C= 0.1 M) of the substrate **s37** (1.3 g, 4.96 mmol, 1 equiv) in THF (49.6 mL) was prepared and cooled to 0°C before LiBH_4 (454 mg, 19.8 mmol, 4 equiv) was added. The reaction mixture was then let stirring at 0°C for 5 hours. The completion of the reaction was monitored by TLC (Pent/EtOAc, 7:3). Total conversion of the substrate was obtained. The reaction was quenched by the slow addition of a diluted aqueous solution of hydrochloric acid (C= 0.1 M). The aqueous layer was extracted with dichloromethane (3x). The combined organic layers were washed with brine (1x), dried

over MgSO₄, filtered in a glass frit and concentrated under vacuum to give a thick yellow oil as the crude product. The latter was then purified by flash column chromatography on silica gel (Pent/EtOAc, 8:2 -> 7:3) to afford the pure product as a white paste (742 mg, 2.81 mmol, 57%).

R_f (Pent/EtOAc, 8:2) = 0.16.

Mp = 57°C.

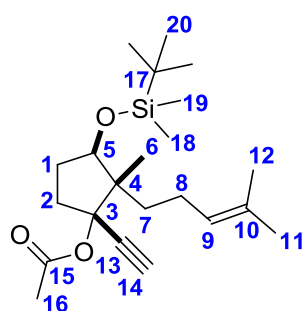
IR (neat): $\tilde{\nu}$ = 3458, 3304 (ν_{OH}), 2967, 2921, 2859 ($\nu_{\text{C-H alkyl}}$), 2113 ($\nu_{\text{C}\equiv\text{C}}$), 1744 ($\nu_{\text{C=O}}$), 1444, 1369 ($\delta_{\text{C-H alkyl}}$), 835 ($\delta_{\text{C-H vinyl}}$), 625 ($\delta_{\text{C-H alkynyl}}$).

¹H NMR (CDCl₃, 400 MHz) δ 5.19-5.08 (m, 1H, H-9), 4.13 (t, ³J = 8.1 Hz, 1H, H-5), 2.65 (s, 1H, H-14), 2.57-2.38 (m, 1H, H-2), 2.38-1.99 (m, 4H, H-1+H-2+H-8), 2.03 (s, 3H, H-16), 1.72-1.49 (m, 3H, H-1+H-7), 1.69 (s, 3H, H-11), 1.62 (s, 3H, H-12), 1.07 (s, 3H, H-6).

¹³C NMR (CDCl₃, 101 MHz) δ 169.3 (C-15), 132.0 (C-10), 125.4 (C-9), 84.9 (C-3), 81.8 (C-13), 78.1 (C-5), 76.1 (C-15), 52.1 (C-4), 34.4 (C-7), 33.4 (C-2), 29.5 (C-1), 25.8 (C-11), 23.2 (C-8), 22.0 (C-16), 17.8 (C-12), 14.9 (C-6).

HRMS (CI) calcd for ([C₁₆H₂₄O₃ + Na]⁺): 287.1618; found: 287.1620.

3-((*tert*-butyldimethylsilyl)oxy)-1-ethynyl-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentyl acetate **s63**



C₂₂H₃₈O₃Si
378.6 .mol⁻¹
Clear yellow oil
89%

The substrate **s58** was introduced (150 mg, 0.568 mmol, 1.0 equiv.) and dissolved in DMF (1 mL). Imidazole (94 mg, 1.36 mmol, 2.4 equiv.), DMAP (7 mg, 0.0568 mmol, 10 mol%) and TBSCl (106 mg, 0.682 mmol, 1.2 equiv.) were successively added at room temperature then the reaction mixture was let stirring overnight. Completion of the reaction was monitored by TLC (PE/Et₂O, 5:5). The reaction was quenched with distilled water. After separation, the aqueous layer was extracted with Et₂O (3x) and the combined organic extracts were washed with distilled water (2x), and brine (2x), then dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to afford a yellow oil as a crude product. The latter was purified by flash column chromatography on silica gel (Pent/Et₂O, 7.5:2.5) so that the pure product was obtained as a clear yellow oil (190 mg, 0.503 mmol, 89%).

R_f (Pent/EtOAc, 7.5:2.5) = 0.55.

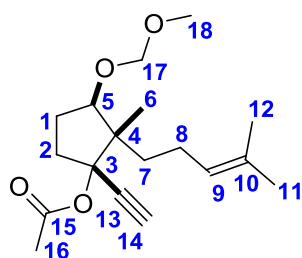
IR (neat): $\tilde{\nu}$ = 3311 ($\nu_{\text{C-H alkynyl}}$), 2955, 2928, 2857 ($\nu_{\text{C-H alkyl}}$), 1747 ($\nu_{\text{C=O}}$), 1463, 1366 ($\delta_{\text{C-H alkyl}}$), 1303 ($\nu_{\text{C-O}}$), 834 ($\delta_{\text{C-H vinyl}}$), 619 ($\delta_{\text{C-H alkynyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 5.10 (m, 1H, H-9), 4.03 (t, $^3J = 8.2$ Hz, 1H, H-5), 2.63 (s, 1H, H-14), 2.48 (m, 1H, H-2), 2.26 (m, 2H, H-2+H-8), 2.02 (m, 4H, H-8+H-16), 1.92 (m, 1H, H-1), 1.69 (s, 3H, H-11), 1.60 (s, 3H, H-12), 1.54 (m, 3H, H-1+H-7), 1.04 (s, 3H, H-6), 0.88 (s, 9H, H-20), 0.05 (H-18 or H-19), 0.03 (H-18 or H-19).

$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ 169.3 (C-5), 131.2 (C-10), 126.0 (C-9), 84.2 (C-5), 82.1 (C-13), 78.7 (C-3), 74.8 (C-14), 52.5 (C-4), 35.0 (C-7), 33.7 (C-2), 29.9 (C-1), 26.0 (C-20), 25.8 (C-11), 23.2 (C-8), 22.1 (C-16), 18.1 (C-17), 17.7 (C-12), 15.2 (C-6), -4.0 (C-18 or C-19), -4.8 (C-18 or C-19).

HRMS (ESI) calcd for $[(\text{C}_{22}\text{H}_{38}\text{O}_3\text{Si} + \text{Na})^+]$: 401.2482; **found**: 401.2494.

1-ethynyl-3-(methoxymethoxy)-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentyl acetate **s67**



$\text{C}_{18}\text{H}_{28}\text{O}_4$
308,4 g.mol⁻¹
Yellow oil
70%

The substrate **s58** (75 mg, 0.284 mmol, 1 equiv.) was introduced as a solution in dichloromethane (2 x 0.47 mL). Then Dipea (0.33 mL, 1.88 mmol, 6.6 equiv.) and MOM-Cl (129 μL , 1.70 mmol, 6 equiv.) were successively added. The reaction mixture was let stirring at room temperature for 5 hours for the conversion to be complete. The completion of the reaction was monitored by TLC (Pent/EtOAc, 7:3). The reaction was quenched by addition of a saturated ammonium chloride aqueous solution. The aqueous layer

was extracted with dichloromethane (3x). The combined organic layers were washed with brine (1x), dried over MgSO_4 , filtered in a glass frit and concentrated under vacuum to afford a yellow oil as the crude product. The latter was purified by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9:1) so that the pure product was obtained as a yellow oil (61 mg, 0.198 mmol, 70%).

R_f (Pent/EtOAc, 7:3) = 0.32.

IR (neat): $\tilde{\nu}$ = 3266 ($\nu_{\text{C-H alkynyl}}$), 2885, 2857 ($\nu_{\text{C-H alkynyl}}$), 2103 ($\nu_{\text{C}\equiv\text{C}}$), 1745 ($\nu_{\text{C=O}}$), 1469, 1441, 1384, 1366 ($\delta_{\text{C-H alkyl}}$), 1304 ($\nu_{\text{C-O}}$), 833 ($\delta_{\text{C-H vinyl}}$), 626 ($\delta_{\text{C-H alkynyl}}$).

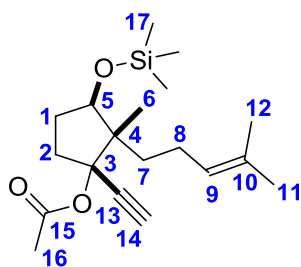
¹H NMR (CDCl₃, 400 MHz) δ 5.15-5.06 (m, 1H, H-9), 4.64 (d, *J* = 6.8 Hz, 1H, H-17), 4.61 (d, *J* = 6.8 Hz, 1H, H-17), 3.94 (t, *J* = 8.3 Hz, 1H, H-5), 3.35 (s, 3H, H-18), 2.64 (s, 1H, H-14), 2.51 (ddd, *J* = 15.1, 9.8, 5.1 Hz, 1H, H-7), 2.26 (ddd, *J* = 15.5, 12.3, 5.8 Hz, 2H, H-7+H-8), 2.14-1.99 (m, 2H, H-8+H-1), 2.02 (s, 3H, H-16), 1.72-1.48 (m, 3H, H-1+H-2), 1.67 (s, 3H, H-11 or H-12), 1.60 (s, 3H, H-11 or H-12), 1.08 (s, 3H, H-6).

¹³C NMR (CDCl₃, 101 MHz) δ 169.2 (C-15), 131.3 (C-10), 125.4 (C-9), 96.5 (C-17), 84.2 (C-3), 83.7 (C-5), 81.6 (C-13), 76.2 (C-14), 55.7 (C-18), 51.9 (C-4), 34.9 (C-2), 33.5 (C-7), 27.2 (C-1), 25.8 (C-11 or C-12), 23.1 (C-8), 22.0 (C-16), 17.7 (C-11 or C-12), 15.5 (C-6).

HRMS (ESI) calcd for [(C₂₁H₄₀O₃Si + Na)⁺]: 391.2639; found: 391.2641.

1-ethynyl-2-methyl-2-(4-methylpent-3-en-1-yl)-3-

((trimethylsilyloxy)cyclopentyl acetate **s66**)



C₁₉H₃₂O₃Si
336.5 g·mol⁻¹
Yellow liquid
97%

The substrate **s58** (100 mg, 0.379 mmol, 1 equiv.) is introduced as a solution in dichloromethane (0.95 mL). Then ClSiMe₃ (85 μL, 0.665 mmol, 1.8 equiv.) and HMDS (90 μL, 0.424 mmol, 1.1 equiv.) were added successively, and the reaction mixture was let stirring at reflux overnight. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 8:2). The reaction was diluted with diethyl ether. The organic layer was washed with brine (3x), dried over MgSO₄, filtered in a glass frit and concentrated under vacuum

to afford a yellow liquid (124 mg, 0.369 mmol, 97%) that was not further purified but engaged as a crude product in the next step.

R_f (*n*-Pent/EtOAc, 9.5:0.5) = 0.43.

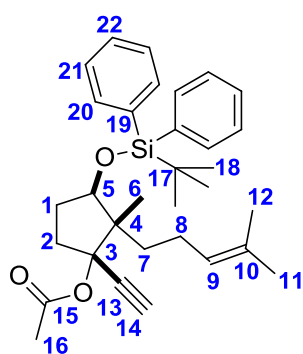
IR (neat): $\tilde{\nu}$ = 3312, 3270 (ν_{C-H alkyne}), 2960, 2915, 2882, 2858 (ν_{C-H alkyne}), 2116 (ν_{C≡C}), 1747 (ν_{C=O}), 1469, 1441, 1369 (δ_{C-H alkyl}), 1303 (ν_{C-O}), 839, 794 (δ_{C-H vinyl}), 622 (δ_{C-H alkyne}).

¹H NMR (CDCl₃, 400 MHz) δ 5.11 (ddt, *J* = 7.1, 4.2, 1.3 Hz, 1H, H-9), 4.04 (t, *J* = 8.3 Hz, 1H, H-5), 2.63 (s, 1H, H-14), 2.48 (ddd, *J* = 15.3, 9.7, 5.4 Hz, 1H, H-2), 2.34-2.17 (m, 2H, H-2+H-8), 2.16-2.01 (m, 1H, H-8), 2.04 (s, 3H, H-16), 1.99-1.85 (m, 1H, H-1), 1.69 (s, 3H, H-11), 1.66-1.42 (m, 3H, H-1+H-7), 1.62 (s, 3H, H-12), 1.03 (s, 3H, H-6), 0.10 (s, 9H, H-17).

13C NMR (CDCl₃, 101 MHz) δ 169.3 (C-15), 131.1 (C-10), 125.7 (C-9), 84.2 (C-3), 82.0 (C-13), 78.7 (C-5), 75.9 (C-14), 52.2 (C-4), 34.9 (C-7), 33.7 (C-2), 29.8 (C-1), 25.8 (C-11), 23.1 (C-8), 22.1 (C-16), 17.8 (C-12), 15.1 (C-6), 0.4 (C-17).

HRMS (ESI) calcd for [(C₁₉H₃₂O₃Si + Na)⁺]: 359.2013; found: 359.2018.

3-((tert-butylidiphenylsilyl)oxy)-1-ethynyl-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentyl acetate **s65**



C₃₂H₄₂O₃Si
502.8 g.mol⁻¹
Yellow oil
74%

The substrate **s58** (100 mg, 0.379 mmol, 1 equiv.) was introduced as a solution in DMF (0.7 mL). Then imidazole (188 mg, 2.73 mmol, 7.2 equiv.), DMAP (14 mg, 0.114 mmol, 30 mol%) and TBDPS-Cl (0.36 mL, 1.37 mmol, 3.6 equiv.) were successively added. The reaction mixture was let stirring overnight at room temperature. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 7:3). The reaction was quenched by the addition of water. After it was separated, the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with water (3x), dried over MgSO₄, filtered in a glass frit and concentrated under vacuum to afford a yellow liquid as the crude product, which was further purified by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9.8:0.2). A yellow oil was obtained (140 mg, 0.279 mmol, 74%).

R_f (*n*-Pent/EtOAc, 9.8:0.2) = 0.27.

IR (neat): $\tilde{\nu}$ = 3310, 3285, 3265 ($\nu_{\text{C-H alkynyl}}$), 2962, 2928, 2891, 2855 ($\nu_{\text{C-H alkynyl}}$), 2117 ($\nu_{\text{C}\equiv\text{C}}$), 1746 ($\nu_{\text{C=O}}$), 1488, 1471, 1462, 1445, 1427, 1364 ($\delta_{\text{C-H alkyl}}$), 1304 ($\nu_{\text{C-O}}$), 823, 807 ($\delta_{\text{C-H vinyl}}$), 610 ($\delta_{\text{C-H alkynyl}}$).

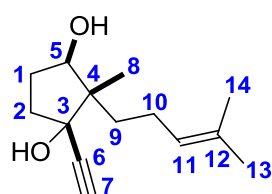
¹H NMR (CDCl₃, 400 MHz) δ 7.80-7.57 (m, 4H, H-20), 7.53-7.31 (m, 6H, H-21+H-22), 5.04 (t, *J* = 6.9 Hz, 1H, H-9), 4.13 (t, *J* = 8.2 Hz, 1H, H-5), 2.64 (s, 1H, H-14), 2.40-1.98 (m, 4H, H-1+H-8), 1.91 (s, 3H, H-16), 1.71 (s, 3H, H-11 or H-12), 1.56 (s, 3H, H-11 or H-12), 1.65-1.37 (m, 4H, H-7+H-2), 1.20 (s, 3H, H-6), 1.10 (s, 9H, H-18).

13C NMR (CDCl₃, 101 MHz) δ 169.2 (C-15), 136.2, 136.1 (C-20), 134.7, 134.0 (C-19), 131.1 (C-10), 129.8, 129.7 (C-21), 127.7, 127.6 (C-22), 125.5 (C-9), 83.7 (C-3), 82.2 (C-13), 79.8 (C-5), 76.1 (C-

14), 52.8 (C-4), 35.1 (C-2), 33.9 (C-1), 29.4 (C-7), 27.2 (C-18), 25.8 (C-11 or C-12), 23.2 (C-8), 21.9 (C-16), 19.5 (C-17), 17.7 (C-11 or C-12), 15.6 (C-6).

HRMS (ESI) calcd for $[(C_{32}H_{42}O_3Si + Na)^+]$: 525.2795; found: 525.2813.

1-ethynyl-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentane-1,3-diol **s60**



$C_{14}H_{22}O_2$
222.3 g.mol⁻¹
Yellow oil

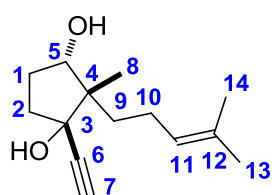
The substrate **s36** (40 mg, 0.182 mmol, 1 equiv.) was dissolved in Et₂O (1.8 mL), so that a yellow solution was obtained, to which LiBH₄ (8 mg, 0.364 mmol, 2 equiv.) was added at 0°C. The heterogeneous mixture so obtained was then stirred at 0°C for 30 minutes. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 7:3), and the reaction was quenched by the addition of a 1M aqueous solution of HCl. The aqueous layer was extracted with DCM (3x). The combined organic layers were washed with brine (1x), dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to afford a yellow oil as the crude product, that was purified by flash column chromatography (*n*-Pent/EtOAc, 8.5:1.5 → 8:2). The pure compound was obtained as a yellow oil.

¹H NMR (CDCl₃, 400 MHz) δ 5.21-5.11 (m, 1H, H-11), 4.18 (t, *J* = 8.0 Hz, 1H, H-5), 2.54 (s, 1H, H-7), 2.35-2.08 (m, 4H, H-10+H-1+H-2), 1.95-1.82 (m, 1H, H-2), 1.72-1.49 (m, 3H, H-9+H-1), 1.70 (s, 3H, H-13), 1.64 (s, 3H, H-14), 1.03 (s, 3H, H-8).

¹³C NMR (CDCl₃, 101 MHz) δ 132.1 (C-12), 125.5 (C-11), 85.9 (C-6), 79.0 (C-3), 78.6 (C-5), 74.0 (C-7), 51.5 (C-4), 37.7 (C-9), 34.2 (C-2), 29.6 (C-1), 25.8 (C-13), 23.2 (C-10), 17.9 (C-14), 15.5 (C-8).

HRMS (ES⁺) calcd for $[(C_{14}H_{22}O_2 + Li)^+]$: 229.1775; found: 229.1779.

1-ethynyl-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentane-1,3-diol **s61**



$C_{14}H_{22}O_2$
222,3 g.mol⁻¹
202 Yellow oil

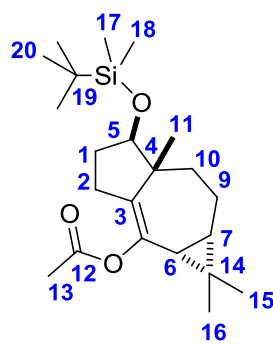
IR (neat): $\tilde{\nu}$ = 3350 (δ_{OH}), 3307 (ν_{C-H} alkynyl), 2968, 2925, 2858 (ν_{C-H} alkyl), 2115 ($\nu_{C\equiv C}$), 1670 ($\nu_{C=C}$), 1462, 1439, 1378 (δ_{C-H} alkyl), 1263 (ν_{C-O}), 1078 (δ_{OH}), 834, 803 (δ_{C-H} vinyl), 631 (δ_{C-H} alkynyl).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 5.26-5.17 (m, 1H, H-11), 3.91-3.86 (m, 1H, H-5), 2.49 (s, 1H, H-7), 2.34-2.00 (m, 5H, H-1+H-2+H-10), 1.93-1.78 (m, 2H, H-2+H-9), 1.70 (s, 3H, H-13), 1.65 (s, 3H, H-14), 1.53 (ddd, $J = 13.6, 11.0, 5.4$ Hz, 1H, H-9), 0.95 (s, 3H, H-8).

$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ 132.0 (C-12), 125.1 (C-11), 84.6 (C-6), 81.0 (C-3), 79.7 (C-5), 73.4 (C-7), 53.4 (C-4), 39.3 (C-1), 31.6 (C-2), 29.5 (C-9), 25.8 (C-13), 23.1 (C-10), 20.9 (C-8), 17.8 (C-14).

HRMS (ES+) calcd for $[(\text{C}_{14}\text{H}_{22}\text{O}_2 + \text{Na})^+]$: 245.1512; found: 245.1517.

5-((*tert*-butyldimethylsilyl)oxy)-1,1,5a-trimethyl-1a,3,4,5,5a,6,7,7a-octahydro-1H-cyclopropa[*f*]azulen-2-yl acetate **s64**



$\text{C}_{22}\text{H}_{38}\text{O}_3\text{Si}$
378,6 g.mol $^{-1}$
Pale yellow oil
70%

The substrate **s66** (75 mg, 0.198 mmol, 1.0 equiv.) was introduced as a solution in dichloromethane (7.9 mL). A clear solution is obtained that is cooled to 0°C before Echavarren's catalyst was added (3.1 mg, 0.00397 mmol, 2 mol%). The solution turns yellow. After a 1.3 h stirring at 0°C, the reaction was complete, as confirmed by TLC (Pent/EtOAc, 9.5:0.5). The reaction mixture was then filtered in glass frit through a short pad of silica and the filtrate concentrated under vacuum to give a yellow oil as the crude product. The latter was further purified by flash column chromatography on silica gel (Pent/EtOAc, 9.8:0.2) to afford the pure product as a pale yellow oil (53 mg, 0.140 mmol, 70%) and as a mixture of two diastereomers in a 5:1 ratio.

mmol, 70%) and as a mixture of two diastereomers in a 5:1 ratio.

IR (neat): $\tilde{\nu} = 2954, 2928, 2857$ ($\nu_{\text{C-H alkynyl}}$), 1751 ($\nu_{\text{C=O}}$), 1701 ($\nu_{\text{C=C}}$), 1461, 1366 ($\delta_{\text{C-H alkyl}}$), 1250 ($\nu_{\text{C-O}}$).

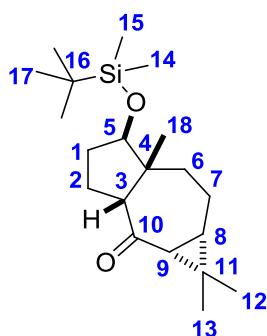
$^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 3.60 (dd, $J = 9.8, 6.9$ Hz, 1H, H-5), 2.18 – 2.12 (m, 2H, H-2), 2.08 (s, 3H, H-13), 1.81 – 1.66 (m, 3H, H-1+H-9+H-10), 1.58 – 1.40 (m, 3H, H-1+H-7+H-10), 1.19 – 0.99 (m, 10H, H-9+H-11+H-15+H-16), 1.00 – 0.85 (m, 10H, H-8+H-20), 0.08 – -0.00 (m, 9H, H-17+H-18).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 169.0 (C-12), 140.2 (C-6), 134.4 (C-3), 79.3 (C-5), 46.6 (C-4), 34.6 (C-10), 29.8 (C-8), 29.4 (C-1), 28.2 (C-11), 26.6 (C-7), 26.0 (C-20), 23.7 (C-2), 21.9 (C-15 or C-16), 21.2 (C-13), 20.8 (C-14), 20.1 (C-9), 18.2 (C-19), 17.0 (C-15 or C-16), -4.1 (C-15 or C-16), -4.9 (C-15 or C-16).

HRMS (ES+) calcd for $[(\text{C}_{22}\text{H}_{38}\text{O}_3\text{Si} + \text{Na})^+]$: 401.2482; found: 401.2480.

5-((*tert*-butyldimethylsilyloxy)-1,1,5a-trimethyloctahydro-1*H*-cyclopropa[*f*]azulen-2(1*aH*)-one

s103



$C_{20}H_{36}O_2Si$
336,6 g.mol⁻¹

To a solution of the substrate **s64** (83 mg, 0.220 mmol, 1 equiv.) in MeOH (4.4 mL), K_2CO_3 (242 mg, 1.76 mmol, 8 equiv.) was added at room temperature so that a heterogeneous orange mixture was obtained, that was stirred at room temperature overnight. The completion of the reaction was monitored by TLC (*n*-Pent/Et₂O, 7:3), and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl . The aqueous layer was extracted with Et₂O (3x). Then, the combined organic layers were washed with brine (1x), dried over $MgSO_4$, filtered through a glass frit and concentrated under vacuum to give a yellow oil as the crude product. The latter was purified by flash column chromatography on silica gel (pure pentane) so that the pure compound was obtained as a yellow oil (20 mg, 0.0594 mmol, 27%).

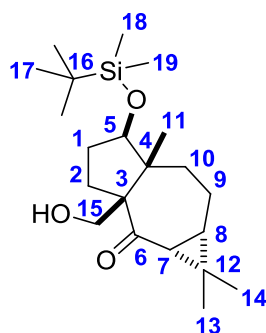
IR (neat): $\tilde{\nu}$ = 2953, 2928, 2857 ($\nu_{C-H \text{ alkyl}}$), 1697 ($\nu_{C=O}$), 1462, 1380 ($\delta_{C-H \text{ alkyl}}$), 1359, 1330, 1253 (ν_{C-O}).

¹H NMR ($CDCl_3$, 400 MHz): δ 3.57 (t, J = 8.1 Hz, 1H, H-**5**), 2.85 (dd, J = 7.9, 2.5 Hz, 1H, H-**3**), 2.01-1.91 (m, 2H, H-**1**+H-**2**), 1.90-1.84 (m, 1H, H-**7**), 1.67-1.56 (m, 2H, H-**1**+H-**2**), 1.51 (d, J = 10.6 Hz, 1H, H-**9**), 1.50-1.44 (m, 1H, H-**1**), 1.43-1.36 (m, 1H, H-**6**), 1.19 (s, 3H, H-**12** or H-**13**), 1.12-1.04 (m, 1H, H-**7**), 1.03 (s, 3H, H-**12** or H-**13**), 1.00 (s, 3H, H-**18**), 0.96-0.90 (m, 1H, H-**8**).

¹³C NMR ($CDCl_3$, 101 MHz): δ 209.5 (C-**10**), 75.3 (C-**5**), 60.3 (C-**3**), 45.7 (C-**4**), 37.7 (C-**9**), 35.0 (C-**6**), 30.4 (C-**1**), 28.4 (C-**12** or C-**13**), 26.7 (C-**8**), 25.9 (C-**17**), 23.4 (C-**18**), 22.6 (C-**11**), 20.9 (C-**2**), 20.4 (C-**7**), 18.1 (C-**16**), 16.7 (C-**12** or C-**13**), -4.2 (C-**14** or C-**15**), -5.0 (C-**14** or C-**15**).

HRMS (ES⁺) calcd for $[(C_{20}H_{36}O_2Si + Na)^+]$: 359.2377; found: 359.2367.

5-((*tert*-butyldimethylsilyloxy)-2a-(hydroxymethyl)-1,1,5a-trimethyloctahydro-1*H*-cyclopropa[*f*]azulen-2(1*aH*)-one s68



C₂₁H₃₈O₃Si
366,6 g.mol⁻¹
White powder
34%

ZnCl₂ (1.4 g; 10 mmol) was dried under high vacuum by mean of a heat gun. A solution of it in dry Et₂O (20 mL; C = 0.5 M) was then prepared. This solution was let stirring under argon and in the dark for 1 h so that a clear grey homogeneous solution was obtained. The substrate **s64** (45 mg; 0.119 mmol; 1 equiv.) was introduced as a solution in Et₂O (1.5 mL). A colourless solution was obtained, to which MeLi (1 M in Et₂O; 0.24 mL; 0.238 mmol; 2 equiv.) was added dropwise at room temperature. After a 10-minute-stirring, a yellow solution was obtained. To it, ZnCl₂ (0.5 M in Et₂O; 0.48 mL; 0.238 mmol; 2 equiv.) was added dropwise at room temperature. Following this addition, a white precipitate was formed. The reaction mixture was let stirring 10 minutes more at room temperature. A pale yellow cloudy solution was obtained. Paraformaldehyde was dried before use. Finally, the latter (18 mg; 0.595 mmol; 5 equiv.) was added rapidly in one single portion at room temperature. After a new 10-minute-stirring at this temperature, the completion of the reaction was monitored by TLC (Pent/EtOAc: 9.5:0.5). Paranisaldehyde was used as the TLC dip. Reaction went to completion. The reaction mixture was quenched with distilled water. The aqueous layer was extracted with Et₂O (3x). The combined organic layers were then washed with distilled water (1x), dried over magnesium sulphate, filtered in a glass frit and concentrated under vacuum to give a yellow oil as the crude product (53 mg). Purification by flash column chromatography (Pent/ EtOAc: 9.8:0.2 -> 7:3) afforded a white residue (15 mg; 0.0409 mmol; 34%) as the pure product.

R_f = 0.29 (*n*-Pent/EtOAc, 8.5/1.5).

Mp: 140°C (the product starts degrading at 110°C).

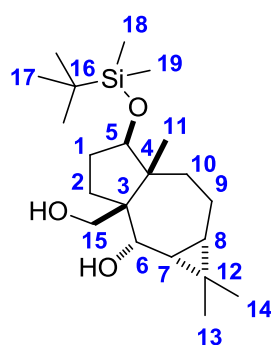
IR (neat): ν = 3400 ($\nu_{\text{free OH}}$ (intermolecular H-bond)), 2954, 2926, 2896, 2856 ($\nu_{\text{C-H alkyl}}$), 1692 ($\nu_{\text{C=O}}$), 1461 ($\delta_{\text{C-H CH}_2}$), 1451, 1437, 1377 ($\delta_{\text{C-H CH}_2}$).

¹H NMR (CDCl₃, 400 MHz) δ 4.37 (d, ²J = 10.7 Hz, 1H, H-15), 3.80 (d, ²J = 10.7 Hz, 1H, H-15), 3.66 (t, ³J = 7.8 Hz, 1H, H-5), 2.42-2.30 (m, 1H, H-2), 2.09-1.96 (m, 1H, H-1), 1.84 (d, ³J = 9.8 Hz, 1H, H-7), 1.81-1.76 (m, 1H, H-10), 1.70-1.57 (m, 1H, H-9), 1.57-1.28 (m, H-2+H-1+H-9), 1.21 (s, 3H, H-13), 1.06 (s, 3H, H-14), 1.03-0.93 (m, 2H, H-10+H-8), 0.87 (s, 3H, H-11), 0.85 (s, 9H, H-17), -0.02 (s, 3H, H-18 or H-19), -0.06 (s, 3H, H-18 or H-19).

¹³C NMR (CDCl₃, 101 MHz) δ 209.9 (C-6), 74.0 (C-5), 67.0 (C-15), 66.1 (C-4), 47.5 (C-3), 34.8 (C-7), 34.0 (C-9), 29.7 (C-1), 28.5 (C-14), 27.7 (C-2), 27.6 (C-8), 25.9 (C-17), 23.0 (C-12), 20.6 (C-10), 18.5 (C-11), 18.1 (C-16), 17.1 (C-13), -4.2 (C-18 or C-19), -5.0 (C-18 or C-19).

HRMS (ES+) calcd for [(C₂₁H₃₈O₃Si + Na)⁺]: 389.2482; **found**: 389.2467.

5-((*tert*-butyldimethylsilyloxy)-2a-(hydroxymethyl)-1,1,5a-trimethyloctahydro-1H-cyclopropa[f]azulen-2(1aH)-one s69



C₂₁H₄₀O₃Si
368,6 g.mol⁻¹
Yellowish powder
50%

The substrate **s68** (146 mg, 0.399 mmol, 1 equiv) was introduced as a solution in dichloromethane (10 ml, C = 0.04 M) so that a pale yellow solution was obtained. At room temperature, the first equivalent of DIBAL-H (0.44 mL, 0.439 mmol, 1.1 equiv) was added dropwise. After a 5 minute-stirring at room temperature, no more H₂ was released from the reaction mixture and the second equivalent of DIBAL-H was added dropwise at room temperature. Again, H₂ was released from the reaction mixture. Then the reaction mixture was heated to reflux and let stirring at 40°C overnight for total conversion to be reached. Completion of the reaction was monitored by TLC (Pent/EtOAc: 8:2). The reaction was quenched by the addition of a diluted aqueous solution of hydrochloric acid (C = 1 M). After separation, the aqueous layer was extracted with Et₂O (3x). The combined organic layers were washed with brine, dried over MgSO₄, filtered in a glass frit and concentrated under vacuum to afford a yellow oil as the crude product. The latter was further purified by flash column chromatography on silica gel (Pent/EtOAc: 8.5:1.5) and the pure product was obtained as a yellowish powder (73 mg, 0.200 mmol, 50%).

R_f = 0.16 (n-Pent/EtOAc, 8.5:1.5).

Mp: 126°C.

IR (neat): ν = 3400 (ν_{OH}), 2955, 2926, 2893, 2883, 2855 (ν_{C-H alkyl}), 1472, 1463, 1453, 1439 (δ_{C-H alkyl}), 1090 (δ_{OH secondary alcohol}), 1047 (δ_{OH primary alcohol}), 1347, 1256 (ν_{C-O}).

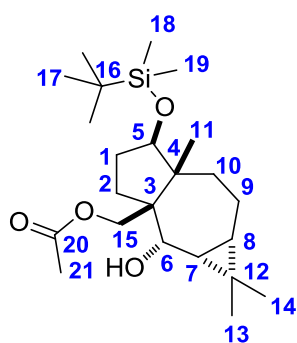
¹H NMR (DMSO-d₆, 400 MHz) δ 4.63 (t, J = 8.1 Hz, 1H, H-5), 4.38 (d, J = 6.5 Hz, 1H, OH_{primary alcohol}), 4.32 (dd, J = 6.5, 4.9 Hz, 1H, H-6), 4.22 (t, J = 4.8 Hz, 1H, OH_{secondary alcohol}), 3.64 (dd, J = 10.3, 5.3 Hz, 1H, H-15), 3.40 (dd, J = 10.3, 4.4 Hz, H-15), 1.95-1.79 (m, 1H, H-1), 1.74-1.51 (m, 4H, H-2 + H-

9 + H-**10**), 1.45 (dt, $J = 12.7, 5.8$ Hz, 1H, H-**9**), 1.33-1.13 (m, 5H, H-**1** + H-**10** + H-**13** or H-**14**), 0.96 (s, 3H, H-**13** or H-**14**), 0.84 (s, 9H, H-**17**), 0.74-0.64 (m, 4H, H-**11** + H-**7**), 0.64-0.51 (m, 1H, H-**8**).

13C NMR (DMSO- d_6 , 101 MHz) δ 74.8 (C-**5**), 74.1 (C-**6**), 65.4 (C-**15**), 54.7 (C-**3** or C-**4**), 49.7 (C-**3** or C-**4**), 34.4 (C-**10**), 32.4 (C-**2**), 30.9 (C-**13** or C-**14**), 30.8 (C-**1**), 28.8 (C-**8**), 26.8 (C-**17**), 25.8 (C-**7**), 21.1 (C-**12**), 19.6 (C-**9**), 19.1 (C-**11**), 17.7 (C-**16**), 16.9 (C-**13** or C-**14**), -4.4 (C-**18** or C-**19**), -4.9 (C-**18** or C-**19**).

HRMS (ES+) calcd for $[(C_{21}H_{40}O_3Si + Na)^+]$: 391.2639; **found**: 391.2639.

(5-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-1,1,5a-trimethyldecahydro-1H-cyclopropa[f]azulen-2a-yl)methyl acetate s75



$C_{23}H_{42}O_4Si$
410,7 g.mol $^{-1}$
White powder
Quant.

The substrate **s69** (60 mg, 0.163 mmol, 1 equiv.) was introduced as a solution in CH_2Cl_2 (1.63 mL) so that a pale yellow solution was obtained. At room temperature, DMAP (3 mg, 0.0245 mmol, 15 mol%), triethylamine (25 μ L, 0.179 mmol, 1.1 equiv.) and acetic anhydride (17 μ L, 0.179 mmol, 1.1 equiv.) were successively added to the reaction mixture, which was then let stirring at room temperature for 30 minutes for total conversion to be reached. Completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 8:2). The reaction was quenched by the addition of water. The aqueous layer was extracted with CH_2Cl_2 (3x), and the combined organic layers were washed with brine (1x), with a 1M aqueous solution of hydrochloric acid (3x), dried over $MgSO_4$, filtered in a glass frit and concentrated under vacuum to afford a white powder as the pure product (67 mg, 0.163 mmol, Quant.).

R_f (*n*-Pent/EtOAc, 9.5:0.5) = 0.28.

R_f (*n*-Pent/EtOAc, 9.8:0.2) = 0.125.

Mp: 140°C.

IR (neat): $\nu = 3514$ (ν_{OH}), 2958, 2927, 2910, 2892, 2857 (ν_{C-H}), 1707 ($\nu_{C=O}$), 1462, 1369 (δ_{C-H} alkyl), 1098 (δ_{OH} secondary alcohol), 1345, 1325, 1299, 1270 (ν_{C-O}).

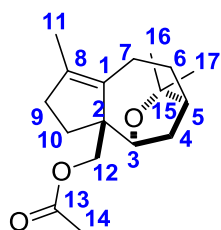
1H NMR ($CDCl_3$, 400 MHz): δ 4.58 (t, $J = 8.2$ Hz, 1H, H-**5**), 4.44 (d, $J = 5.0$ Hz, 1H, H-**6**), 4.22 (d, $J = 11.2$ Hz, 1H, H-**15**), 4.17 (d, $J = 11.2$ Hz, 1H, H-**15**), 2.04 (s, 3H, H-**21**), 2.01-1.89 (m, 1H, H-**1**), 1.84-1.68 (m, 4H, H-**2**+H-**10**), 1.68-1.54 (m, 2H, H-**9**), 1.51-1.28 (m, 1H, H-**1**), 1.33 (s, 3H, H-**13** or H-**14**),

1.02 (s, 3H, H-13 or H-14), 0.87 (s, 9H, H-17), 0.82 (s, 3H, H-11), 0.73 (td, $J = 9.5, 5.9$ Hz, 1H, H-8), 0.54-0.45 (m, 1H, H-7), -0.01 (s, 6H, H-18+H-19).

^{13}C NMR (CDCl_3 , 101 MHz): δ 171.4 (C-20), 77.6 (C-6), 75.0 (C-5), 69.9 (C-15), 53.4 (C-3), 51.0 (C-4), 34.6 (C-2), 32.5 (C-10), 31.1 (C-1), 31.0 (C-13 or C-14), 29.8 (C-8), 27.6 (C-7), 26.0 (C-17), 22.5 (C-12), 21.2 (C-2), 20.0 (C-9), 19.8 (C-11), 18.2 (C-16), 17.1 (C-13 or C-14), -4.2 (C-18 or C-19), -4.8 (C-18 or C-19).

HRMS (ES+) calcd for $[(\text{C}_{23}\text{H}_{42}\text{O}_4\text{Si} + \text{Na})^+]$: 433.2745; found: 433.2740.

(3,3,7-trimethyl-1,3,4,5,6,8,9,9a-octahydro-1,4-methanocyclopenta[c]oxocin-9a-yl)methyl acetate *s76*



$\text{C}_{17}\text{H}_{26}\text{O}_3$
278,4 g.mol $^{-1}$
Yellow oil
34%

To a solution of the substrate *s75* (47 mg, 0.115 mmol, 1 equiv.) in DCM (2 mL), pyridine (19 μL , 0.230 mmol, 2 equiv.) and Tf_2O (39 μL , 0.230 mmol, 2 equiv.) were successively added. A dark orange solution was obtained, that was stirred at room temperature for 24h. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 9:1). A brown mixture was obtained. The reaction was quenched by the addition of water. The aqueous layer was extracted with dichloromethane (3x). Then, the combined organic layers were washed with brine (2x), dried over MgSO_4 ,

filtered through a glass frit and concentrated under vacuum to give the crude product as an orange oil. The latter was purified by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9:1) to yield the pure product as a yellow oil (11 mg, 0.0395 mmol, 34%).

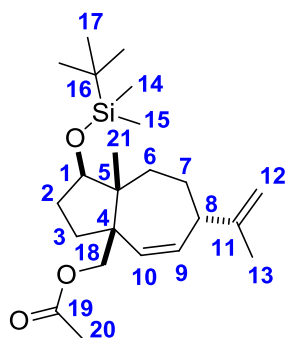
IR (neat): $\nu = 2968, 2924, 2858$ ($\nu_{\text{C-H}}$), 1742 ($\nu_{\text{C=O}}$), 1692 ($\nu_{\text{C=C}}$), 1472, 1454, 1437, 1380 ($\delta_{\text{C-H alkyl}}$), 1298 ($\nu_{\text{C-O}}$).

^1H NMR (CDCl_3 , 400 MHz): δ 4.09 (d, $J = 8.2$ Hz, 1H, H-3), 4.00 (d, $J = 9.8$ Hz, 1H, H-12), 3.97 (d, $J = 9.8$ Hz, 1H, H-12), 2.38-2.16 (m, 4H, H-9 +H-4+H-7), 2.14-1.99 (m, 2H, H-4+H-5), 2.02 (s, 3H, H-14), 1.89-1.76 (m, 1H, H-7), 1.76-1.65 (m, 3H, H-10 +H-6), 1.65-1.53 (m, 1H, H-6), 1.63 (s, 3H, H-11), 1.18 (s, 3H, H-16 or H-17), 1.06 (s, 3H, H-16 or H-17).

^{13}C NMR (CDCl_3 , 101 MHz): δ 171.5 (C-13), 137.2 (C-8), 133.4 (C-1), 83.3 (C-15), 81.8 (C-3), 68.1 (C-12), 58.4 (C-2), 43.7 (C-5), 36.5 (C-9), 31.9 (C16 or C-17), 29.4 (C-4), 28.4 (C-10), 25.7 (C-6), 25.2 (C-16 or C-17), 21.6 (C-7), 21.1 (C-14), 14.2 (C-11).

HRMS (ES+) calcd for $[(\text{C}_{17}\text{H}_{26}\text{O}_3 + \text{Na})^+]$: 301.1774; found: 301.1762.

(1-((*tert*-butyldimethylsilyl)oxy)-8a-methyl-6-(prop-1-en-2-yl)-1,2,3,3a,6,7,8,8a-octahydroazulen-3a-yl)methyl acetate s81



C₂₃H₄₀O₃Si
392,6 g.mol⁻¹
Yellow oil
Quant.

The substrate **s75** (20 mg, 0.0488 mmol, 1 equiv.) was dissolved in dichloromethane (2 mL). At 0°C, triethylamine (136 µL, 0.976 mmol, 20 equiv.), DMAP (24 mg, 0.195 mmol, 4 equiv.) and MsCl (58 µL, 0.732 mmol, 15 equiv.) were successively added. Then, the reaction mixture was let stirring at room temperature overnight. After the completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 9:1), the reaction was quenched by the addition of a saturated aqueous solution of NaHCO₃. After separation, the aqueous layer was extracted with EtOAc (3x). Then, the combined organic layers were washed with brine (1x), dried over MgSO₄, filtered

through a glass frit and concentrated under vacuum to afford a brown crude product that was purified by flash column chromatography on silica gel(*n*-Pent/EtOAc, 9.8:0.2) to yield the pure product as a yellow oil (19 mg, 0.0488 mmol, Quant.).

R_f = 0.18 (*n*-Pent/EtOAc, 9.8:0.2).

IR (neat): ν = 2956, 2930, 2857 (ν_{C-H}), 1745 ($\nu_{C=O}$), 1647 ($\nu_{C=C}$), 1469 (δ_{C-H} alkyl), 1400 (δ_{C-H} vinyl), 1375 (δ_{C-H} alkyl), 889, 668 (δ_{C-H} vinyl).

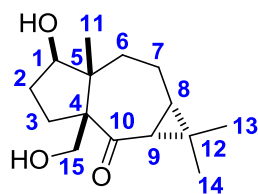
¹H NMR (CDCl₃, 300 MHz): δ 5.48 (dd, J = 12.3, 3.5 Hz, 1H, H-**9**), 5.23 (dd, J = 12.3, 2.7 Hz, 1H, H-**10**), 4.75-4.67 (m, 2H, H-**12**), 4.23 (t, J = 7.9 Hz, 1H, H-**1**), 4.17 (d, J = 10.9 Hz, 1H, H-**18**), 4.04 (d, J = 10.9 Hz, 1H, H-**18**), 2.98-2.89 (m, 1H, H-**8**), 2.06 (s, 3H, H-**20**), 2.00-1.89 (m, 1H, H-**2**), 1.88-1.62 (m, 4H, H-**6**, H-**3**, H-**7**), 1.60-1.36 (m, 3H, H-**3**, H-**2**, H-**7**), 1.73 (s, 3H, H-**13**), 0.90 (s, 3H, H-**21**), 0.88 (s, 9H, H-**17**), 0.03 (s, 3H, H-**14** or H-**15**), 0.02 (H-**14** or H-**15**).

¹³C NMR (CDCl₃, 75 MHz): δ 171.2 (C-**19**), 150.2 (C-**11**), 137.4 (C-**10**), 135.1 (C-**9**), 109.6 (C-**12**), 75.7 (C-**1**), 69.2 (C-**18**), 50.8 (C-**5**), 47.8 (C-**4**), 47.5 (C-**8**), 35.9 (C-**6**), 34.9 (C-**3**), 29.1 (C-**2**), 28.0 (C-**7**), 26.0 (C-**17**), 21.3 (C-**20**), 20.4 (C-**13**), 18.8 (C-**21**), 18.1 (C-**16**), -4.02 (C-**14** or C-**15**), -4.8 (C-**14** or C-**15**).

HRMS (ESI) calcd for [(C₂₃H₄₀O₃ + Na)⁺]:415.2639; found:415.2653.

5-hydroxy-2a-(hydroxymethyl)-1,1,5a-trimethyloctahydro-1H-cyclopropa[f]azulen-2(1aH)-one

s70



$C_{15}H_{24}O_3$
252,3 g.mol⁻¹
White crystals
64%

The substrate **s68** (340 mg, 0.929 mmol, 1 equiv.) was dissolved in THF (3.3 mL). To the clear solution so obtained, TBAF (0.45 mL, 0.45 mmol, 1.5 equiv.) was added at room temperature. The solution turned yellow, and then was let stirring at room temperature overnight. After the completion of the reaction was monitored by TLC (Pent/EtOAc, 1:1), the reaction mixture was adsorbed on silica and purified by flash column chromatography on silica gel (Pent/EtOAc, 1:1) to yield white crystals as

the pure product (149 mg, 0.591 mmol, 64%).

$R_f = 0.25$ (*n*-Pent/EtOAc, 1:1).

Mp = 180°C.

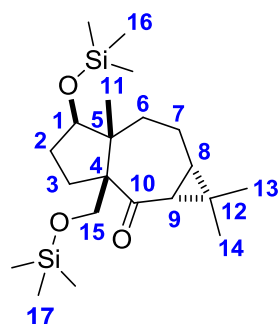
IR (neat): $\tilde{\nu} = 3378$ (ν_{OH}), 2951, 2921, 2864, 2852 (ν_{C-H} alkyl), 1692 ($\nu_{C=O}$), 1483, 1454, 1438, 1377 (δ_{C-H} alkyl), 1324, 1284 (ν_{C-O}).

¹H NMR (CDCl₃, 300 MHz): δ 4.41 (dd, $J = 10.4, 5.0$ Hz, 1H, H-**15**), 3.89-3.78 (m, 1H, OH), 3.77-3.62 (m, 2H, OH+H-**15**), 3.57 (d, $J = 5.7$ Hz, 1H, H-**1**), 2.38-2.21 (m, 1H, H-**3**), 2.01-1.87 (m, 2H, H-**2**+H-**9**), 1.82-1.67 (m, 2H, H-**7**+H-**6**), 1.54-1.35 (m, 3H, H₂+H-**7**+H-**3**), 1.16 (s, 3H, H-**13** or H-**14**), 1.08-0.91 (m, 2H, H-**6**+H-**8**), 1.02 (s, 3H, H-**11**), 0.85 (s, 3H, H-**13** or H-**14**).

¹³C NMR (CDCl₃, 75 MHz): δ 209.8 (C-**10**), 73.3 (C-**1**), 67.2 (C-**5**), 66.5 (C-**15**), 47.3 (C-**4**), 35.4 (C-**9**), 34.6 (C-**7**), 29.9 (C-**2**), 28.7 (C-**11**), 28.6 (C-**3**), 28.1 (C-**8**), 23.2 (C-**12**), 21.2 (C-**6**), 18.6 (C-**13** or C-**14**), 17.4 (C-**13** or C-**14**).

HRMS (ESI) calcd for [(C₁₅H₂₄O₃ + Na)⁺]: 275.1618; found: 275.1627.

1,1,5a-trimethyl-5-((trimethylsilyl)oxy)-2a-(((trimethylsilyl)oxy)methyl)octahydro-1H-cyclopropa[f]azulen-2(1aH)-one **s71**



$C_{21}H_{40}O_3Si_2$
396,7 g.mol⁻¹
White crystals
77%

The substrate **s70** (20 mg, 0.0794 mmol, 1 equiv.) was dissolved in dichloromethane (2 mL). HMDS (17 μ L, 0.0794 mmol, 1 equiv.) and TMSCl (1 drop) were successively added at room temperature. Then, the reaction mixture was heated to 40°C and let stirring at this temperature overnight. After the completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 1:1), the reaction was diluted with Et₂O, then washed with brine (3x), dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to yield white crystals as the crude product. The latter was purified by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9:1), and the pure product was obtained as white crystals (24 mg, 0.0605 mmol, 77%).

$R_f = 0.89$ (*n*-Pent/EtOAc, 9:1). $R_f = 0.19$ (*n*-Pent/EtOAc, 9.8:0.2).

Mp = 92°C.

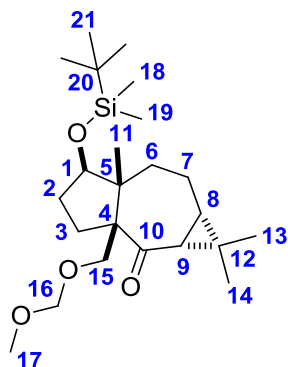
IR (neat): $\tilde{\nu} = 2956, 2918, 2897, 2864$ ($\nu_{C-H \text{ alkyl}}$), 1690 ($\nu_{C=O}$), 1464, 1438, 1378 ($\delta_{C-H \text{ alkyl}}$), 1354 (ν_{C-O}).

¹H NMR (CDCl₃, 300 MHz): δ 4.34 (d, $J = 9.8$ Hz, 1H, H-**15**), 3.70-3.63 (m, 1H, H-**1**), 3.60 (d, $J = 10$ Hz, 1H, H-**15**), 2.38-2.20 (m, 1H, H-**3**), 2.11-1.93 (m, 1H, H-**2**), 1.87-1.69 (m, 2H, H-**9**+H-**7**), 1.62 (dd, $J = 14.5, 7.0$ Hz, 1H, H-**6**), 1.48-1.27 (m, 3H, H-**2**+H-**3**+H-**6**), 1.22 (s, 3H, H-**13** or H-**14**), 1.05 (s, 3H, H-**13** or H-**14**), 1.02-0.84 (m, 2H, H-**7**+H-**8**), 0.82 (s, 3H, H-**11**), 0.07 (s, 3H, H-**16** or H-**17**), 0.02 (s, 9H, H-**16** or H-**17**).

¹³C NMR (CDCl₃, 75 MHz): δ 210.1 (C-**10**), 73.5 (C-**1**), 66.6 (C-**15**), 65.6 (C-**4**), 46.9 (C-**5**), 34.7 (C-**9**), 33.8 (C-**6**), 29.9 (C-**2**), 29.7 (C-**3**), 28.6 (C-**13** or C-**14**), 27.5 (C-**8**), 23.0 (C-**12**), 20.7 (C-**7**), 18.5 (C-**11**), 17.0 (C-**13** or C-**14**), 0.3 (C-**16** or C-**17**), -0.4 (C-**16** or C-**17**).

HRMS (ES+) calcd for $[(C_{21}H_{40}O_3Si_2 + Na)^+]$: 419.2408; **found**: 419.2409.

5-((*tert*-butyldimethylsilyl)oxy)-2a-((methoxymethoxy)methyl)-1,1,5a-trimethyloctahydro-1H-cyclopropa[f]azulen-2(1aH)-one **s72**



C₂₃H₄₂O₄Si
410,7 g.mol⁻¹
Yellow oil
68%

The substrate **s68** (50 mg, 0.137 mmol, 1 equiv.) was dissolved in dichloromethane (2 mL). A yellow solution was obtained, to which diisopropylethylamine (0.30 mL, 1.80 mmol, 13 equiv.) and MOMCl (124 μ L, 1.64 mmol, 12 equiv.) were successively added. The reaction mixture was then heated at 40°C and let stirring at this temperature for 6.5 h. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 8.5:1.5). Once finished, the reaction was quenched by the addition of a saturated aqueous solution of NH₄Cl. After separation, the aqueous layer was extracted with dichloromethane (3x), and the combined organic layers were washed with brine (1x), dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to

afford a yellow crude product that was purified by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9.8:0.2 -> 9.5:0.5). The pure product was obtained as a yellow oil (38 mg, 0.0927 mmol, 68%).

R_f = 0.30 (*n*-Pent/EtOAc, 9.5:0.5).

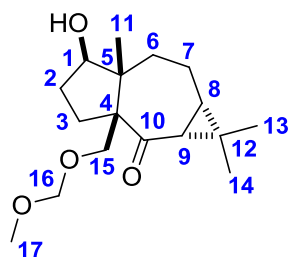
IR (neat): $\tilde{\nu}$ = 2953, 2927, 2884, 2857 ($\nu_{\text{C-H alkyl}}$), 1694 ($\nu_{\text{C=O}}$), 1463, 1438, 1379 ($\delta_{\text{C-H alkyl}}$), 1324 ($\nu_{\text{C-O}}$).

¹H NMR (CDCl₃, 400 MHz): δ 4.67-4.53 (m, 2H, H-**16**), 4.31 (d, *J* = 9.2 Hz, 1H, H-**15**), 3.66 (t, *J* = 8.1 Hz, 1H, H-**1**), 3.59 (d, *J* = 9.2 Hz, 1H, H-**15**), 3.33 (s, 3H, H-**17**), 2.45-2.27 (m, 1H, H-**2**), 2.10-1.95 (m, 1H, H-**3**), 1.85-1.71 (m, 2H, H-**7**+H-**9**), 1.71-1.57 (m, 1H, H-**6**), 1.56-1.31 (m, 3H, H-**2**+H-**3**+H-**6**), 1.21 (s, 3H, H-**11**), 1.04 (s, 3H, H-**13** or H-**14**), 1.01-0.89 (m, 2H, H-**7**+H-**8**), 0.85 (s, 3H, H-**13** or H-**14**), 0.84 (s, 9H, H-**21**), -0.032 (s, 3H, H-**18** or H-**19**), -0.073 (s, 3H, H-**18** or H-**19**).

¹³C NMR (CDCl₃, 100 MHz): δ 209.4 (C-**10**), 97.1 (C-**16**), 73.3 (C-**1**), 72.4 (C-**15**), 64.5 (C-**5**), 55.8 (C-**17**), 47.4 (C-**4**), 34.4 (C-**9**), 33.8 (C-**6**), 29.7 (C-**3**), 28.7 (C-**2**), 28.6 (C-**13** or C-**14**), 27.8 (C-**8**), 25.9 (C-**21**), 23.1 (C-**12**), 20.6 (C-**7**), 18.7 (C-**13** or C-**14**), 18.1 (C-**20**), 17.0 (C-**11**), -4.2 (C-**18** or C-**19**), -5.0 (C-**18** or C-**19**).

HRMS (ESI) calcd for [(C₂₃H₄₂O₄Si + Na)⁺]:319.1880; found:319.1878.

5-hydroxy-2a-((methoxymethoxy)methyl)-1,1,5a-trimethyloctahydro-1H-cyclopropa[f]azulen-2(1aH)-one *s73*



$C_{17}H_{28}O_4$
296,4 g.mol⁻¹
White crystals
86%

The substrate *s72* (37 mg, 0.0902 mmol, 1 equiv.), was dissolved in THF (1 mL). Then TBAF (0.14, 0.143 mmol, 1.5 equiv.) was added at room temperature, and the reaction mixture was let stirring in dark at this temperature overnight. After the completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 1:1), the reaction mixture was adsorbed on silica and purified by flash column chromatography on silica gel (*n*-Pent/EtOAc, 7:3) to give the pure product as white crystals (23 mg, 0.0777 mmol, 86%).

$R_f = 0.26$ (*n*-Pent/EtOAc, 7:3).

Mp = 97°C.

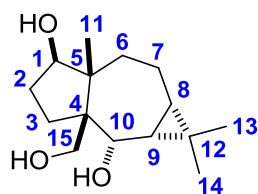
IR (neat): $\tilde{\nu} = 3450$ (ν_{OH}), 2948, 2920, 2864 (ν_{C-H} alkyl), 1692 ($\nu_{C=O}$), 1467, 1455, 1439, 1376 (δ_{C-H} alkyl), 1324, 1261 (ν_{C-O}), 1104 (δ_{OH}).

¹H NMR (CDCl₃, 400 MHz): δ 4.66-4.54 (m, 2H, H-**16**), 4.29 (d, *J* = 9.2 Hz, 1H, H-**15**), 3.74 (t, *J* = 8.2 Hz, 1H, H-**1**), 3.60 (d, *J* = 9.2 Hz, 1H, H-**15**), 3.33 (s, 3H, H-**17**), 2.45-2.30 (m, 1H, H-**6**), 2.24-2.09 (m, 1H, H-**2**), 1.89-1.64 (m, 3H, H-**7**+H-**3**+H-**9**), 1.56-1.36 (m, 3H, H-**6**+H-**2**+H-**3**), 1.20 (s, 3H, H-**13** or H-**14**), 1.04 (s, 3H, H-**13** or H-**14**), 1.03-0.91 (m, 2H, H-**7**+H-**8**), 0.88 (s, 3H, H-**11**).

¹³C NMR (CDCl₃, 100 MHz): δ 209.1 (C-**10**), 97.1 (C-**16**), 73.5 (C-**1**), 72.1 (C-**15**), 65.0 (C-**9**), 55.9 (C-**17**), 46.7 (C-**4**), 34.4 (C-**9**), 33.9 (C-**3**), 29.6 (C-**2**), 28.5 (C-**11**), 28.4 (C-**6**), 27.8 (C-**8**), 23.2 (C-**12**), 20.5 (C-**7**), 18.2 (C-**13** or C-**14**), 17.0 (C-**13** or C-**14**).

HRMS (ESI) calcd for [(C₁₇H₂₈O₄ + Na)⁺]:433.2745; found:433.2748.

2a-(hydroxymethyl)-1,1,5a-trimethyldecahydro-1H-cyclopropa[f]azulene-2,5-diol **s74**



$C_{15}H_{26}O_3$
254,4 g.mol⁻¹
White foam
73%

The substrate **s69** (66 mg, 0.179 mmol, 1 equiv.) was dissolved in THF (2 mL). A clear solution was obtained, to which TBAF (0.27 mL, 0.269 mmol, 1.5 equiv.) was added at room temperature. The solution turned green, then brown, after a few minutes, and was let stirring at room temperature overnight. The completion of the reaction was monitored by TLC (Pent/EtOAc, 1:1), after what the reaction mixture was adsorbed on silica and the crude product purified by flash column chromatography on silica gel (Pent/EtOAc, 7:3). The pure product was obtained as a white foam (33 mg, 0.130 mmol, 73%).

$R_f = 0.16$ (*n*-Pent/EtOAc, 1:1).

Mp = 63°C.

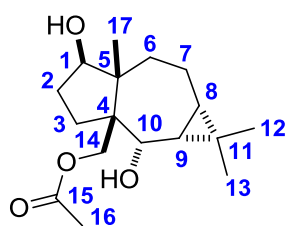
IR (neat): $\tilde{\nu} = 3380$ (ν_{OH}), 2954, 2923, 2894, 2859 (ν_{C-H} alkyl), 1484, 1465, 1441, 1375 (δ_{C-H} alkyl), 1344, 1279, 1261 (ν_{C-O}).

¹H NMR (CDCl₃, 300 MHz): δ 4.60 (t, *J* = 8.3 Hz, 1H, H-**1**), 4.51 (d, *J* = 4.0 Hz, 1H, H-**10**), 3.88 (d, *J* = 10.7 Hz, 1H, H-**15**), 3.69 (d, *J* = 10.7 Hz, 1H, H-**15**), 2.22-2.08 (m, 1H, H-**2**), 1.85-1.61 (m, 5H, H-**3**+H-**6**+H-**7**), 1.51-1.35 (m, 2H, H-**2**+H-**3**), 1.33 (s, 3H, H-**13** or H-**14**), 1.04 (s, 3H, H-**13** or H-**14**), 0.83 (s, 3H, H-**11**), 0.80-0.65 (m, 3H, H-**8**+H-**9**).

¹³C NMR (CDCl₃, 75 MHz): δ 77.6 (C-**10**), 75.8 (C-**1**), 68.2 (C-**15**), 55.6 (C-**4** or C-**5**), 50.2 (C-**4** or C-**5**), 35.0 (C-**3**), 32.1 (C-**6**), 31.0 (C-**2**), 29.5 (C-**8** or C-**9**), 27.8 (C-**8** or C-**9**), 22.5 (C-**12**), 19.9 (C-**7**), 19.0 (C-**11**), 17.0 (C-**13** or C-**14**).

HRMS (ESI) calcd for [(C₁₅H₂₆O₃ + Na)⁺]: 277.1774; found: 277.1774.

(2,5-dihydroxy-1,1,5a-trimethyldecahydro-1H-cyclopropa[f]azulen-2a-yl)methyl acetate **s93**



C₁₇H₂₈O₄
296,4 g.mol⁻¹
White solid
57%

The substrate **s74** (30 mg, 0.118 mmol, 1 equiv.), was dissolved in dichloromethane (3 mL) to afford a clear solution to which DMAP (2 mg, 0.0177 mmol, 15 mol%), triethylamine (18 μL, 0.130 mmol, 1.1 equiv.) and acetic anhydride (12 μL, 0.130 mmol, 1.1 equiv.) were successively added at room temperature. The reaction mixture was let stirring at room temperature for 1 h, and the completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 7:3).

The reaction was quenched by the addition of water. After separation, the aqueous layer was extracted with dichloromethane (3x). Then, the combined organic layers were dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to give a yellow oil as the crude product. After purification by flash column chromatography on silica gel (*n*-Pent/EtOAc, 7:3 → 1:1), the pure product was obtained as a white solid (20 mg, 0.0676 mmol, 57%).

R_f = 0.16 (*n*-Pent/EtOAc, 7:3). R_f = 0.45 (*n*-Pent/EtOAc, 1:1).

Mp = 154°C.

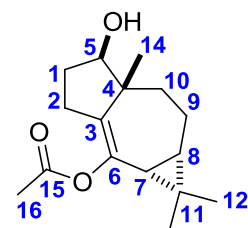
IR (neat): $\tilde{\nu}$ = 3500, 3430 (ν_{OH}), 2956, 2918, 2862 (ν_{C-H alkyl}), 1720 (ν_{C=O}), 1463, 1389 (δ_{C-H alkyl}), 1364, 1272 (ν_{C-O}).

¹H NMR (CDCl₃, 300 MHz): δ 4.64 (t, *J* = 8.4 Hz, 1H, H-**1**), 4.45 (d, *J* = 4.6 Hz, 1H, H-**10**), 4.20 (d, *J* = 2.8 Hz, 2H, H-**14**), 2.15 (dtd, *J* = 13.8, 9.7, 5.1 Hz, 1H, H-**2**), 2.05 (s, 3H, H-**16**), 1.86-1.70 (m, 2H, H-**3**+H-**6**), 1.70-1.57 (m, 1H, H-**8**), 0.50 (dd, *J* = 9.1, 5.0 Hz, 1H, H-**9**).

¹³C NMR (CDCl₃, 75 MHz): δ 171.4 (C-**15**), 77.7 (C-**10**), 75.4 (C-**1**), 69.6 (C-**14**), 53.9 (C-**4** or C-**5**), 34.8 (C-**6**), 32.2 (C-**3**), 31.0 (C-**12** or C-**13**), 30.9 (C-**2**), 29.6 (C-**8**), 27.5 (C-**9**), 22.6 (C-**11**), 21.2 (C-**16**), 19.9 (C-**7**), 19.3 (C-**17**), 17.0 (C-**12** or C-**13**).

HRMS (ESI) calcd for [(C₁₇H₂₈O₄ + Na)⁺]: 319.1880; found: 319.1868.

5-hydroxy-1,1,5a-trimethyl-1a,3,4,5,5a,6,7,7a-octahydro-1H-cyclopropa[f]azulen-2-yl acetate **s105**



To a stirred solution of the substrate **s64** (35 mg, 0.0926 mmol, 1 equiv.) in THF (1mL) cooled at 0°C, TBAF (268 μL, 0.931 mmol, 10 equiv.)

Experimental Part

C₁₆H₂₄O₃
264,4 g.mol⁻¹

was added dropwise. Then, the reaction mixture was stirred at 50°C overnight. The completion of the reaction was monitored by TLC (PE/Et₂O, 1:1), after what the reaction mixture was concentrated under vacuum to afford a brown oil as the crude product. The latter was purified by flash column chromatography on silica gel (PE/Et₂O, 1:1).

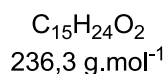
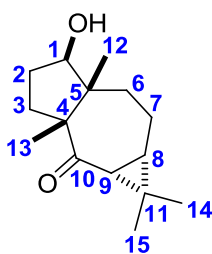
IR (neat): $\tilde{\nu}$ = 3438 (ν_{OH}), 2925, 2864 ($\nu_{\text{C-H alkyl}}$), 1749 ($\nu_{\text{C=O}}$), 1700 ($\nu_{\text{C=C}}$), 1465, 1369 ($\delta_{\text{C-H alkyl}}$), 1108 ($\delta_{\text{OH secondary alcohol}}$).

¹H NMR (400 MHz, Chloroform-d) δ 3.67 (dd, J = 9.8, 6.8 Hz, 1H, H-5), 2.22-2.14 (m, 2H, H-2), 2.08 (s, 3H, H-16), 1.94-1.38 (m, 6H, H-10+H-1+H-7+H-9), 1.22-1.12 (m, 1H, H-9), 1.09 (s, 3H, H-14), 1.02 (s, 3H, H-12 or H-13), 1.02 (s, 3H, H-12 or H-13), 0.98-0.88 (m, 1H, H-8).

¹³C NMR (101 MHz, CDCl₃) δ 169.0 (C-15), 140.6 (C-3 or C-6), 134.4 (C-3 or C-6), 79.9 (C-5), 45.9 (C-4), 34.7 (C-10), 29.4 (C-1), 29.3 (C-8), 28.2 (C-12 or C-13), 26.5 (C-7), 23.7 (C-2), 21.5 (C-14), 21.1 (C-16), 20.9 (C-11), 20.3 (C-9), 16.9 (C-12 or C-13).

HRMS (ESI) calcd for [(C₁₆H₂₄O₃ + Na)⁺]:287.1618; found:287.1625.

5-hydroxy-1,1,2a,5a-tetramethyloctahydro-1H-cyclopropa[f]azulen-2(1aH)-one **s101**



To a stirred solution of the substrate **s64** (254 mg, 0.672 mmol, 1 equiv.) in DME (2.7 mL) cooled at -50°C, MeLi (0.84 mL, 1.34 mmol, 2 equiv.) was added dropwise. The reaction mixture was stirred at -50°C for 5 min before HMPA (0.23 mL, 1.34 mmol, 2 equiv.) was added dropwise, followed by the addition of MeI (1.05 mL, 16.8 mmol, 25 equiv.). The reaction mixture was stirred at -50°C for more 5 min. Then, the completion of the reaction was monitored by TLC (*n*-Pent/Et₂O, 8.5:1.5) and the reaction mixture was poured into a saturated aqueous solution of NH₄Cl cooled at 0°C. The

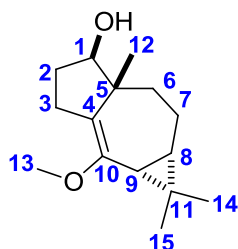
aqueous layer was extracted with Et₂O (3x) and the resulting combined organic layers dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to give the crude product as a pale yellow oil. Purification by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9.8:0.2) afforded the titled compound. The latter was dissolved in THF (1.8 mL, C = 0.0926 M) so that a pale yellow solution was obtained, to which TBAF (1.66 mL, 1.66 mmol, 10 equiv.) was added at room temperature. Then, the reaction mixture was heated to 50°C and stirred at this temperature overnight. The completion of the reaction was monitored by TLC (*n*-Pent/Et₂O, 1:1). The reaction mixture was concentrated under vacuum to give the crude product as an orange oil that was purified by flash column chromatography on silica gel (*n*-Pent/Et₂O, 5.5:4.5).

¹³C NMR (101 MHz, CDCl₃) δ 211.9 (C-10), 73.4 (C-1), 60.2 (C-4), 48.1 (C-5), 34.4 (C-9), 33.3 (C-7), 31.1 (C-3), 30.0 (C-2), 28.5 (C-14), 28.0 (C-8), 26.0 (C-19), 23.3 (C-11), 20.6 (C-6), 19.9 (C-13), 18.3 (C-12), 18.1 (C-18), 17.0 (C-15), -4.2 (C-16 or C-17), -5.0 (C-16 or C-17).

¹H NMR (CDCl₃, 400 MHz) δ 3.68 (dd, *J* = 8.6, 7.5 Hz, 1H, H-1), 2.19-2.08 (m, 1H, H-3), 2.07-1.95 (m, 1H, H-2), 1.81-1.60 (m, 3H, H-7+H-6+H-9), 1.44-1.22 (m, 3H, H-7+H-3+H-2), 1.27 (s, 3H, H-13), 1.19 (s, 3H, H-14), 0.93-0.82 (m, 2H, H-6+H-8), 0.85 (s, 9H, H-19), -0.03 (s, 3H, H-16 or H-17), -0.07 (s, 3H, H-16 or H-17).

HRMS (ES+) calcd for ([C₁₅H₂₄O₂ + Na]⁺):259.1669; found:259.1663.

2-methoxy-1,1,5a-trimethyl-1a,3,4,5,5a,6,7,7a-octahydro-1H-cyclopropa[f]azulen-5-ol s102

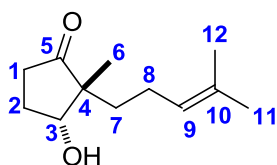


C₁₅H₂₄O₂
236,3 g.mol⁻¹

¹H NMR (CDCl₃, 400 MHz) δ 3.61-3.49 (m, 1H, H-1), 3.52 (s, 3H, H-13), 2.40-2.30 (m, 1H, H-3), 2.15 (dddd, *J* = 17.2, 9.8, 8.6, 2.7 Hz, 1H, H-3), 1.85-1.58 (m, 3H, H-6+H-2+H-7), 1.57-1.38 (m, 2H, H-6+H-2), 1.22-1.12 (m, 2H, H-9+H-7), 1.11 (s, 3H, H-14 or H-15), 1.01 (s, 3H, H-14 or H-15), 0.97 (s, 3H, H-12), 0.95-0.83 (m, 1H, H-8), 0.89 (s, 3H, H-19), 0.0026 (s, 6H, H-16+H-17).

¹³C NMR (101 MHz, CDCl₃) δ 145.0 (C-10), 124.9 (C-4), 80.7 (C-1), 54.7 (C-13), 45.7 (C-5), 35.4 (C-6), 30.0 (C-2), 28.7 (C-8), 27.9 (C-14 or C-15), 26.0 (C-19), 24.9 (C-9), 23.6 (C-3), 22.5 (C-12), 20.5 (C-7), 20.2 (C-11), 18.2 (C-18), 16.8 (C-14 or C-15), -4.1 (C-16 or C-17), -4.8 (C-16 or C-17).

3-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentanone s110



C₁₂H₂₀O₂
Experimental
Yellow oil
93%

The substrate s13 (1.5 g, 7.73 mmol, 1.0 equiv.) was dissolved in THF (65.7 mL). The solution so obtained was cooled to 0°C and LiAlH(OtBu)₃ (11.6 mL, 11.6 mmol, 1.5 equiv.) was added dropwise at

this temperature. The reaction mixture was then let stirring for 3 hours at 0°C. Completion of the reaction was monitored by TLC (Pent/Et₂O, 60:40). The reaction was quenched by addition of saturated NH₄Cl aqueous solution. The aqueous layer was extracted with Et₂O. Then the combined organic layers were dried over MgSO₄, filtered in a glass frit and concentrated under vacuum to give a light yellow oil as a crude product, which was further purified by flash column chromatography on silica gel (Pent/EtOAc, 8:2 -> 5:5) to afford a yellow oil as a mixture of 2 diastereomers in a 5:1 ratio (1.4 g, 7.14 mmol, 93%).

R_f (*n*-Pent/EtOAc, 8:2) = 0.23.

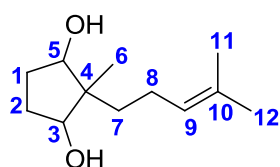
IR (neat): $\tilde{\nu}$ = 3435 (ν_{OH}), 2965, 2917 ($\nu_{\text{C-H}}$), 1724 ($\nu_{\text{C=O}}$), 1620 ($\nu_{\text{C=C}}$), 1455, 1375 ($\delta_{\text{C-H alkyl}}$), 1256 ($\nu_{\text{C-O}}$), 1106 (δ_{OH}), 833 ($\delta_{\text{C-H vinyl}}$), 622 ($\delta_{\text{C-H alkynyl}}$).

¹H NMR (CDCl₃, 400 MHz): δ 5.11 (ddq, J = 7.1, 5.7, 1.4 Hz, 1H, H-9), 4.2 (t, J = 4.4 Hz, 1H, H-3), 2.51-2.34 (m, 1H, H-2), 2.32-1.77 (m, 5H, H-1+H-2+H-7), 1.65 (s, 3H, H-11), 1.58 (s, 3H, H-12), 1.56-1.47 (m, 2H, H-8), 0.98 (s, 3H, H-6).

¹³C NMR (CDCl₃, 101 MHz): δ 221.2 (C-5), 132.6 (C-10), 124.3 (C-9), 77.5 (C-3), 53.3 (C-4), 34.1 (C-2), 30.2 (C-8), 27.7 (C-1), 25.7 (C-11), 22.4 (C-7), 19.2 (C-6), 17.7 (C-12).

HRMS (ES⁺) calcd for [(C₁₂H₂₀O₂ + Na)⁺]:219.1356; found:219.1353.

2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentane-1,3-diol **s112**



C₁₂H₂₂O₂
198,3 g.mol⁻¹
Yellow oil
33%

To a stirred solution of the substrate **s13** (53 mg, 0.273 mmol, 1 equiv.) in MeOH (1.4 mL) cooled at -10°C, CeCl₃·7H₂O (112 mg, 0.301 mmol, 1.1 equiv.) and NaBH₄ (12 mg, 0.301 mmol, 1.1 equiv.) were successively added and the reaction mixture was stirred at -10°C for 25 minutes. The completion of the reaction was monitored by TLC (*n*-Pent/Et₂O, 4:6). The reaction was quenched by the addition of a 1M aqueous solution of HCl. The aqueous layer was extracted with Et₂O

(3x). The combined organic layers were washed with brine (1x), dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to afford the crude product as a yellow oil. Purification by flash column chromatography (*n*-Pent/Et₂O, 4:6) gave the pure product as a yellow oil (18 mg, 0.0908, 33%).

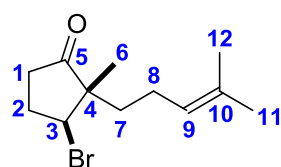
IR (neat): $\tilde{\nu}$ = 3376 (ν_{OH}), 2965, 2925, 2857 ($\nu_{\text{C-H}}$), 1672 ($\nu_{\text{C=C}}$), 1460, 1377 ($\delta_{\text{C-H alkyl}}$), 1288 ($\nu_{\text{C-O}}$), 1100 (δ_{OH}), 842 ($\delta_{\text{C-H vinyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 5.29-5.17 (m, 1H, H-9), 3.83-3.77 (m, 2H, H-3+H-5), 2.37-2.30 (m, 2H, 2 x OH), 2.19-2.02 (m, 4H, H-1+H-2+H-7), 1.96-1.79 (m, 2H, H-1+H-2), 1.72-1.60 (m, 2H, H-8), 1.69 (s, 3H, H-12), 1.64 (s, 3H, H-11), 0.78 (s, 3H, H-6).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 132.0 (C-10), 125.2 (C-9), 80.7 (C-3+C-5), 50.3 (C-4), 32.0 (C-1+C-2), 30.9 (C-8), 25.8 (C-12), 23.3 (C-7), 21.1 (C-6), 17.8 (C-11).

HRMS (ES+) calcd for $[(\text{C}_{12}\text{H}_{22}\text{O}_2 + \text{Na})^+]$: 221.1512; found: 221.1511.

3-bromo-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentanone **s113**



$\text{C}_{12}\text{H}_{19}\text{BrO}$
259.2 $\text{g}\cdot\text{mol}^{-1}$
Yellow oil
45%

The substrate **s110** (51mg, 0.260 mmol, 1.0 equiv.) was dissolved into THF (1.63 mL). Then triphenylphosphine (138 mg, 0.520 mmol, 2.0 equiv.) and carbon tetrabromide (176 mg, 0.520 mmol, 2.0 equiv.) were successively added at 0°C , and the reaction mixture was let stirring at this temperature for 3 hour. Completion of the reaction was monitored by TLC (Pent/ Et_2O ,6:4). The reaction mixture was diluted with Et_2O , filtered through Celite then concentrated under vacuum to give a yellowish solid as a crude product. Purification by flash column chromatography on silica gel afforded the pure product as a yellow oil (30 mg, 0.116 mmol, 45%).

$R_f = 0.32$ (*n*-Pent/ Et_2O , 9.2:0.8).

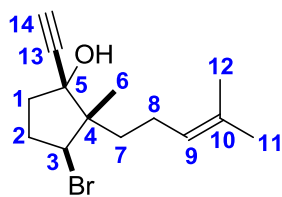
IR (neat): $\tilde{\nu} = 2968, 2924, 2855$ ($\nu_{\text{C-H}}$), 1742 ($\nu_{\text{C=O}}$), 1450, 1376 ($\delta_{\text{C-H alkyl}}$), 1630 ($\nu_{\text{C=C}}$), 1264 ($\nu_{\text{C-O}}$), 832, 794 ($\delta_{\text{C-H vinyl}}$), 600 ($\nu_{\text{C-Br}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 5.11-4.97 (m, 1H, H-9), 4.52-4.40 m, 1H, H-3), 2.67-2.43 m, 2H, H-1+H-2), 2.43-2.11 (m, 2H, H-1+H-2), 2.09-1.76 (m, 2H, H-8), 1.66 (s, 3H, H-11), 1.63-1.52 (m, 4H, H-7+H-9), 1.47 (ddd, $J = 14.0, 11.1, 5.5$ Hz, 1H, H-7), 1.11 (s, 3H, H-6).

$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz): δ 216.5 (C-5), 132.6 (C-10), 123.5 (C-9), 56.1 (C-3), 53.6 (C-4), 36.3 (C-1), 34.6 (C-7), 30.2 (C-2), 25.8 (C-11), 23.1 (C-8), 20.6 (C-12), 17.8 (C-6).

HRMS (ESI) calcd for $[(\text{C}_{12}\text{H}_{19}\text{BrO} + \text{Na})^+]$: 281.0511; found: 281.0515.

3-bromo-1-ethynyl-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentanol **s115**



$C_{14}H_{21}BrO$
 $285.2 \text{ g}\cdot\text{mol}^{-1}$
 Yellow oil
 80%

A suspension of $CeCl_3$ (1.7 g, 6.76 mmol, 7 equiv.) in THF (17 mL) was prepared and let stirring at room temperature for 2 hours. At -78°C , ethynylmagnesium bromide (27.6 mL, 5.79 mmol, 6 equiv.) was added *via* syringe under argon. The reaction mixture was let stirring at -78°C under argon for 1 hour, then the substrate **s113** (250 mg, 0.965 mmol, 1 equiv.) was added as a solution in THF. Finally, the reaction mixture was let warming slowly back to room temperature overnight.

A coffee-like mixture was obtained. Completion of the reaction was monitored by TLC (PE/EtOAc, 7.5:2.5). The reaction was quenched by the addition of water. After separation, the aqueous layer was extracted with Et_2O (3x). Then the combined organic layers were washed with brine (1x), dried over $MgSO_4$, filtered in a glass frit, and concentrated under vacuum to afford a thick brown oil as the crude product, which was further purified by flash column chromatography on silica gel (Pent/Et $2O$, 8.5:1.5). The pure product was obtained as a yellow oil (221 mg, 0.776 mmol, 80%).

$R_f = 0.23$ (*n*-Pent/ Et_2O , 8.5:1.5).

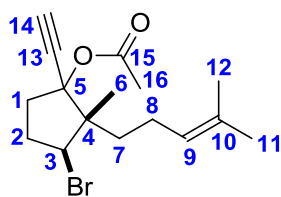
IR (neat): $\tilde{\nu} = 3457, 3289$ (ν_{OH}), 2977, 2914, 2879, 2854 (ν_{C-H}), 2107 ($\nu_{C\equiv C}$), 1671 ($\nu_{C=C}$), 1468, 1443, 1379 ($\delta_{C-H \text{ alkyl}}$), 1343, 1305, 1268 (ν_{C-O}), 1097 (δ_{OH}), 833, 787 ($\delta_{C-H \text{ vinyl}}$), 624 ($\delta_{C-H \text{ vinyl}}$).

1H NMR ($CDCl_3$, 400 MHz): δ 5.19-5.08 (m, 1H, H-9), 4.23-4.10 (m, 1H, H-3), 2.60 (s, 1H, H-14), 2.52 (s, 1H, OH), 2.41-2.25 (m, 1H, H-2), 2.28-1.99 (m, 5H, H-1+H-2+H-7), 1.76-1.51 (m, 8H, H-8+H-11+H-12), 1.08 (s, 3H, H-6).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 132.1 (C-10), 125.3 (C-11), 86.1 (C-13), 76.4 (C-5), 74.7 (C-14), 59.2 (C-3), 51.0 (C-4), 38.7 (C-1), 36.8 (C-8), 31.0 (C-2), 25.7 (C-11), 23.0 (C-7), 17.8 (C-12), 15.0 (C-6).

3-bromo-1-ethynyl-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentyl acetate **s116**

Ac_2O (2.1 mL, 22.5 mmol, 32.0 equiv.) and DMAP (61 mg, 0.491 mmol, 70 mol%) were successively introduced. Then the substrate **s115** (200 mg, 0.702 mmol, 1.0 equiv.) was



$C_{16}H_{23}BrO_2$
327.3 $g \cdot mol^{-1}$
Yellow oil
57%

introduced as a solution in pyridine (1.8 mL). The reaction mixture was heated to 100°C and let stirring at this temperature for 24h. The orange solution turns brown when heated. Completion of the reaction was monitored by TLC (Pent/ Et₂O, 8:2). The reaction mixture was diluted with water and after separation, the aqueous layer was extracted with Et₂O (3x). Then the combined organic layers were washed with a saturated NaHCO₃ aqueous solution (3x), and with

water (1x) and brine (1x), dried over MgSO₄, filtered in a glass frit and concentrated under vacuum to give a thick brown oil as a crude product, which was further purified by flash column chromatography on silica gel (Pent/Et₂O, 9.8:0.2) to afford a yellow oil as the pure product (131 mg, 0.401 mmol, 57%).

$R_f = 0.27$ (*n*-Pent/Et₂O, 9.8:0.2).

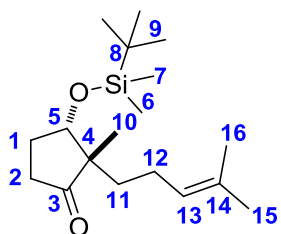
IR (neat): $\tilde{\nu} = 3290$ (ν_{OH}), 2967, 2914, 2856 (ν_{C-H}), 2113 ($\nu_{C=C}$), 1750 ($\nu_{C=O}$), 1469, 1443, 1381, 1367 ($\delta_{C-H alkyl}$), 1311, 1272 (ν_{C-O}), 834, 797 ($\delta_{C-H vinyl}$), 626 ($\delta_{C-H vinyl}$).

¹H NMR (CDCl₃, 400 MHz): δ 5.17-5.07 (m, 1H, H-9), 4.16 (t, $J = 8.8$ Hz, 1H, H-3), 2.87-2.72 (m, 1H, H-1), 2.64 (s, 1H, H-14), 2.48-2.31 (m, 1H, H-2), 2.29-1.99 (m, 7H, H-1+H-2+H-8+H-16), 1.79-1.50 (m, 8H, H-7+H-11+H-12), 1.15 (s, 3H, H-6).

¹³C NMR (CDCl₃, 101 MHz): δ 169.0 (C-15), 131.7 (C-10), 124.7 (C-9), 82.0 (C-13), 80.7 (C-5), 75.8 (C-14), 57.6 (C-3), 51.6 (C-4), 36.9 (C-7), 36.6 (C-1), 25.8 (C-11), 22.7 (C-8), 21.7 (C-16), 17.8 (C-12), 15.3 (C-6).

HRMS (ESI) calcd for [(C₁₆H₂₃BrO₂ + Na)⁺]: 350.08072; found: 350.08081.

3-((tert-butyldimethylsilyl)oxy)-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentanone **s117**



$C_{18}H_{34}O_2Si$
310.5 $g \cdot mol^{-1}$

To a stirred solution of the substrate **s110** (2.4 g, 12.2 mmol, 2 equiv.) in DMF (11 mL), imidazole (2 g, 29.4 mmol, 4.8 equiv.), DMAP (302 mg, 2.44 mmol, 40 mol%) and TBSCl (2.2 g, 14.7 mmol, 2.4 equiv.) were successively added. Then, the reaction mixture was heated to 35°C and stirred overnight at this temperature. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 1:1). The reaction was quenched by the addition of water. The aqueous layer was extracted with Et₂O (3x). The combined organic layers were washed with water (1x), dried over MgSO₄,

filtered through a glass frit and concentrated under vacuum to give the crude product as a yellow oil. Purification by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9.8/0.2) afforded the pure product.

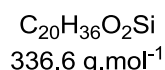
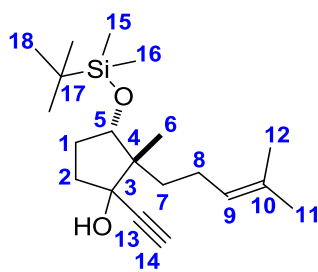
IR (neat): $\tilde{\nu}$ = 2950, 2920, 2850 ($\nu_{\text{C-H}}$), 1735 ($\nu_{\text{C=O}}$), 1250 ($\nu_{\text{C-O}}$), 834 ($\delta_{\text{C-H vinyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 5.05 (t, J = 6.3 Hz, 1H, H-**13**), 4.02 (t, J = 5.4 Hz, 1H, H-**5**), 2.41 (ddd, J = 17.9, 9.8, 5.8, 1H, H-**2**), 2.28-1.75 (m, 5H, H-**2**+H-**1**+H-**12**), 1.66 (s, 3H, H-**15** or H-**16**), 1.63-1.49 (m, 1H, H-**11**), 1.58 (s, 3H, H-**15** or H-**16**), 1.42 (ddd, J = 13.8, 12.1, 5.3 Hz, 1H, H-**11**), 0.99 (s, 3H, H-**10**), 0.89 (s, 3H, H-**9**), 0.09 (s, 3H, H-**6** or H-**7**), 0.08 (s, 3H, H-**6** or H-**7**).

$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ 220.7 (C-**3**), 131.6 (C-**14**), 124.6 (C-**13**), 78.5 (C-**5**), 53.4 (C-**4**), 34.5 (C-**2**), 30.6 (C-**11**), 28.4 (C-**1**), 25.9 (C-**9**), 25.8 (C-**15** or C-**16**), 22.6 (C-**12**), 19.4 (C-**10**), 18.1 (C-**8**), 17.8 (C-**15** or C-**16**), -4.2 (C-**6** or C-**7**), -4.8 (C-**6** or C-**7**).

HRMS (ESI) calcd for $[(\text{C}_{18}\text{H}_{34}\text{O}_2\text{Si} + \text{Li}]^+$: 317.2483; **found**: 317.2480.

3-((*tert*-butyldimethylsilyl)oxy)-1-ethynyl-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentanol



A suspension of CeCl_3 (9.5 g; 38.4 mmol; 7 equiv.) in THF (96 mL) was prepared, which was let stirring at room temperature for 2 h. To the white suspension so obtained, ethynyl magnesium bromide (66 mL; 32.9 mmol; 8 equiv.) was added at -78°C . The reaction mixture was let stirring at this temperature for one more hour before the substrate **s117** (1.7 g; 5.48 mmol; 1 equiv.) was added at -78°C . Finally, the reaction mixture was let warming to room temperature overnight. The completion of the reaction was monitored by TLC (Pent/EtOAc, 8:2). The reaction mixture was quenched with a diluted aqueous solution of hydrochloric acid ($\text{C} = 1\text{M}$). The aqueous layer was extracted with Et_2O (2x). Then the combined organic layers were washed with brine (1x), dried over magnesium, filtered in a glass frit and concentrated under vacuum to afford a brownish solid as the crude product (1.7 g). The latter was purified by flash column chromatography (Pent/EtOAc, 9.8:0.2).

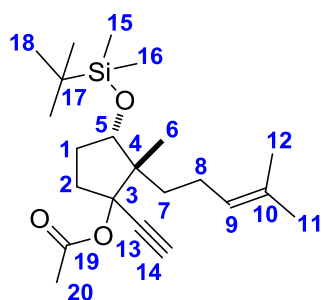
IR (neat): $\tilde{\nu}$ = 3472, 3266 (ν_{OH}), 2964, 2957, 2949, 2938, 2928, 2880, 2855 ($\nu_{\text{C-H}}$), 1735 ($\nu_{\text{C=O}}$), 1472, 1462, 1447, 1439, 1376 ($\delta_{\text{C-H alkyl}}$), 1343, 1315, 1262 ($\nu_{\text{C-O}}$), 1093 (δ_{OH}), 842, 831, 817 ($\delta_{\text{C-H vinyl}}$), 646 ($\delta_{\text{C-H alkynyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 5.11 (t, $^3J = 8.2$ Hz, 1H, H-9), 3.95 (d, $^3J = 5.0$ Hz, 1H, H-5), 2.41 (s, 1H, H-14), 2.35-2.27 (m, 2H, H-2), 2.27-2.14 (m, 1H, H-8), 2.14-2.04 (m, 1H, H-1), 1.96-1.82 (m, 1H, H-8), 1.82-1.70 (m, 2H, H-1+H-7), 1.67 (s, 3H, H-11), 1.64-1.53 (m, 1H, H-7), 1.61 (s, 3H, H-12), 0.94 (s, 3H, H-6), 0.87 (s, 9H, H-21), 0.09 (s, 3H, H-19 or H-20), 0.07 (s, 3H, H-19 or H-20).

$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ 131.1 (C-10), 125.1 (C-9), 85.0 (C-13), 81.1 (C-5), 80.6 (C-3), 72.4 (C-14), 53.4 (C-4), 40.2 (C-2), 31.5 (C-1), 29.9 (C-7), 25.8 (C-18), 23.2 (C-8), 20.8 (C-4), 17.9 (C-12), -4.3 (C-15 or C-16), -5.1 (C-15 or C-16).

HRMS (ESI) calcd for $[(\text{C}_{20}\text{H}_{36}\text{O}_2\text{Si} + \text{Na})^+]$: 359.2377; found: 359.2363.

3-((*tert*-butyldimethylsilyloxy)-1-ethynyl-2-methyl-2-(4-methylpent-3-en-1-yl)cyclopentyl acetate **s119**



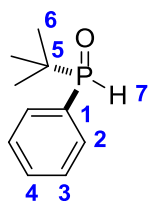
$\text{C}_{22}\text{H}_{38}\text{O}_3\text{Si}$
378,6 g.mol $^{-1}$

IR (neat): $\tilde{\nu} = 3307$ ($\nu_{\text{C-H alkynes}}$), 2955, 2929, 2886, 2857 ($\nu_{\text{C-H alkyl}}$), 2115 ($\nu_{\text{C}\equiv\text{C}}$), 1719 ($\nu_{\text{C=O}}$), 1462, 1383 ($\delta_{\text{C-H alkyl}}$), 1317 ($\nu_{\text{C-O}}$), 833 ($\delta_{\text{C-H vinyl}}$), 622 ($\delta_{\text{C-H alkynes}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 5.06 (tq, $J = 6.1, 1.4$ Hz, 1H, H-9), 3.97 (dd, $J = 6.8, 4.4$ Hz, 1H, H-5), 2.68-2.56 (m, 2H, H-14 + H-2), 2.56-2.44 (m, 1H, H-2), 2.29 (s, 3H, H-20), 2.18-2.06 (m, 2H, H-1 + H-8), 2.05-1.94 (m, 1H, H-8), 1.80-1.59 (m, 5H, H-1 + H-7 + H-11), 1.57 (s, 3H, H-12), 1.50 (ddd, $J = 13.6, 12.5, 5.1$ Hz, 1H, H-7), 1.11 (s, 3H, H-6), 0.82 (s, 9H, H-18), 0.02 (s, 3H, H-15 or H-16), 0.01 (s, 3H, H-15 or H-16).

$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ 194.5 (C-19), 131.4 (C-10), 125.2 (C-9), 85.7 (C-3), 82.5 (C-13), 78.9 (C-5), 75.4 (C-14), 53.3 (C-4), 36.1 (C-2), 31.5 (C-1), 30.5 (C-7), 25.8 (C-11), 25.7 (C-18), 25.3 (C-20), 23.5 (C-8), 21.2 (C-6), 18.0 (C-17), 17.8 (C-12), -4.3 (C-15 or C-16), -4.9 (C-15 or C-16).

(\pm)-*tert*-butyl(phenyl)phosphine oxide **m3**



$\text{C}_{10}\text{H}_{15}\text{OP}$
182,2 g.mol $^{-1}$
White solid
76%

A suspension of *t*-BuMgCl (0.8 M in Et_2O , 38 mL, 45.8 mmol, 1.0 equiv.) in Et_2O (27 mL) was prepared. To this grey suspension, PPhCl_2 (7.7 mL, 55 mmol, 1.2 equiv.) was added dropwise at 0°C . During this addition, the reaction mixture became white. It was let stirring at reflux for 18 hours. Then it was quenched by the dropwise addition of a 6 M aqueous solution of hydrochloric acid. The aqueous phase was extracted with dichloromethane (3 x 30 mL). Then the combined organic layers were washed with brine (120 mL), dried over MgSO_4

and filtered in a frit to give a yellow oil as the crude product, the distillation of which at 150°C under vacuum (5 mbar) afforded the pure product as a white solid (6.3 g, 34.6 mmol, 76%).

$R_f = 0.30$ (Et₂O/MeOH, 96:4).

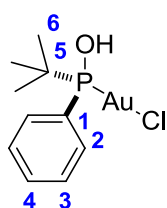
Mp: 56°C.

IR (neat): $\nu = 3055$ ($\nu_{\text{C-H aryl}}$), 2964, 2902, 2867 ($\nu_{\text{C-H alkyl}}$), 1591, 1474, 1438 ($\nu_{\text{C=C Ar}}$), 1394, 1365 ($\delta_{\text{C-H tert-butyl}}$), 1166 ($\nu_{\text{P=O}}$), 747, 696 ($\delta_{\text{C-H aryl}}$).

¹H NMR (CDCl₃, 300 MHz) δ 6.94 (d, $J = 452.8$ Hz, 1H, H-7), 7.59 (m, 2H, H-2), 7.53 – 7.34 (m, 3H, H-3 + H-4), 1.05 (d, $J = 16.6$ Hz, 9H, H-6).

¹³C NMR (CDCl₃, 75 MHz) δ 132.4 (d, $J = 2.8$ Hz, C-4), 130.8 (d, $J = 10.0$ Hz, C-2), 128.9 (d, $J = 89.9$ Hz, C-1), 128.4 (d, $J = 11.9$ Hz, C-3), 31.9 (d, $J = 69.2$ Hz, C-5), 23.4 (d, $J = 2.1$ Hz, C-6).

³¹P NMR (CDCl₃, 162 MHz) δ 47.9.



m6

C₁₀H₁₅AuClOP
414,6 g.mol⁻¹
White powder
88%

t-BuPhP(O)H **m3** (1.0 g, 5.49 mmol, 1.0 equiv.) was introduced as a solution in dichloromethane (5 x 1 mL). Then the volume of dichloromethane was completed to 65 mL via syringe. A colorless solution was obtained, to which ClAu.SMe₂ (1.6 g, 5.49 mmol, 1.0 equiv.) was added. The solution turned pale yellow in colour. The reaction mixture was let stirring protected from light

at room temperature under an argon atmosphere. After 2 hours, it was concentrated under vacuum to afford a brownish foam which was then re-dissolved into a minimum of dichloromethane (3 mL), and pentane (30 mL) was added to it in order to make the complex precipitate. After Büchner filtration, the complex was obtained pure as a white powder and dried further under vacuum (2.033g, 4.90 mmol, 88%).

Mp: 178°C.

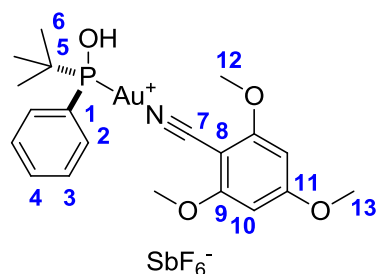
IR (neat): $\nu = 3124$ (ν_{OH}), 2961, 2866 ($\nu_{\text{C-H alkyl}}$), 1474, 1459 ($\nu_{\text{C=C aryl}}$), 1393, 1364 ($\delta_{\text{C-H tert-butyl}}$), 748, 695 ($\delta_{2 \text{ contiguous C-H aryl}}$).

¹H NMR (CDCl₃, 400 MHz) δ 7.70 – 7.59 (m, 2H, H-2), 7.50 – 7.41 (m, 1H, H-4), 7.41 – 7.31 (m, 2H, H-3), 1.07 (d, $J = 17.7$ Hz, 9H, H-6).

¹³C NMR (CDCl₃, 101 MHz) δ 132.1 (d, $J = 2.8$ Hz, C-4), 131.9 (d, $J = 14.6$ Hz, C-2), 131.4 (d, $J = 62.0$ Hz, C-1), 128.4 (d, $J = 12.1$ Hz, C-3), 35.3 (d, $J = 46.7$ Hz, C-5), 24.6 (d, $J = 6.6$ Hz, C-6).

^{31}P NMR (CDCl_3 , 162 MHz) δ 110.9.

HRMS (ES+) calcd for $(\text{C}_{10}\text{H}_{15}\text{AuClOP} + \text{Na})^+$: 437.0107; found: 437.0124.



m35

$\text{C}_{20}\text{H}_{26}\text{AuF}_6\text{NO}_4\text{PSb}$
808,1 $\text{g}\cdot\text{mol}^{-1}$
Grey crystals
Quant.

t-BuPhP(OH)AuCl **m6** (415 mg, 1.0 mmol, 1.0 equiv.) was introduced with 2,4,6-trimethoxybenzotrile (197 mg, 1.0 mmol, 1.0 equiv.). Both were dissolved in dichloromethane (11 mL). Then AgSbF_6 (351 mg, 1.0 mmol, 1.0 equiv.) was added and, instantly, a white precipitate appeared. The reaction mixture was let stirring for an additional 15 minute-time under an argon atmosphere and protected from light before filtration over a Teflon membrane afforded a yellow solution that was concentrated under vacuum. The crude product was obtained as a white foam. The latter was then dissolved into a minimum

of dichloromethane (3 mL), and an equivalent volume of pentane (3 mL) was slowly added to the surface so that the resulting solution was biphasic. Overnight crystallization in these conditions gave grey crystals as the pure complex (808 mg, 1.0 mmol, quant.).

Mp: 170°C.

IR (neat): ν = 3608 (ν_{OH}), 2956 ($\nu_{\text{C-H}}$ alkyl), 2249 (ν_{CN} aryl nitrile), 1603, 1576 ($\nu_{\text{C=C}}$ aryl), 1477, 1460, 1437, 1421, 1353 ($\delta_{\text{C-H}}$ -CH₃), 751.09, 697.16 ($\delta_{\text{C-H}}$ aryl).

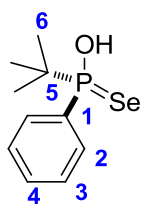
^1H NMR (CD_2Cl_2 , 400 MHz) δ 7.79 – 7.67 (m, 2H, H-**2**), 7.65 – 7.49 (m, 3H, H-**3**), 6.13 (s, 2H, H-**10**), 3.91 (s, 6H, H-**12**), 3.89 (s, 3H, H-**13**), 1.16 (d, J = 18.3 Hz, 9H, H-**6**).

^{13}C NMR (CD_2Cl_2 , 101 MHz) δ 169.7 (C-**11**), 166.6 (C-**9**), 133.6 (d, J = 3.0 Hz, C-**4**), 132.3 (d, J = 14.6 Hz, C-**2**), 129.9 (d, J = 66.3 Hz, C-**1**), 129.4 (d, J = 12.5 Hz, C-**3**), 119.8 (C-**7**), 91.7 (C-**10**), 57.2 (C-**12**), 56.9 (C-**13**), 35.7 (d, J = 48.0 Hz, C-**5**), 24.5 (d, J = 6.4 Hz, C-**6**).

^{31}P NMR (CD_2Cl_2 , 162 MHz) δ 113.6.

HRMS (ES+) calcd for $(\text{C}_{20}\text{H}_{26}\text{AuNO}_4\text{P})^+$: 572.125948; found: 572.127231.

(±)-*tert*-butyl(phenyl)phosphinoselenoic O-acid **m40**



$C_{10}H_{15}OPSe$
 $261,2 \text{ g}\cdot\text{mol}^{-1}$
 Yellowish solid
 66%

t-BuPhP(O)H **m3** (50 mg, 0.275 mmol, 1 equiv) was introduced as a solution in $CDCl_3$ (5.5 mL). Elemental selenium (166 mg, 2.09 mmol, 7.6 equiv.) was added as a powder, followed by triethylamine (0.15 mL, 1.05 mmol, 3.8 equiv.). The reaction mixture was heated to 62°C and it was let stirring at this temperature for 4 h. The reaction mixture was concentrated under vacuum to afford a black residue to which water was added. The aqueous layer so obtained was acidified by addition of a diluted aqueous solution of hydrochloric acid ($C = 1\text{M}$) and extracted with $CDCl_3$ (3x). The combined organic layers were dried over $MgSO_4$, filtered in a glass frit and concentrated under vacuum to yield a yellowish solid (48 mg, 0.182 mmol, 66%) as a crude product which was not further purified.

IR (neat): $\nu = 2960, 2945, 2924, 2900, 2866, 2853$ ($\nu_{C-H \text{ alkyl}}$), $1588, 1573, 1475, 1459$ ($\nu_{C=C \text{ Ar}}$), 1436 ($\delta_{C-H \text{ alkyl}}$), $748, 694$ ($\delta_{C-H \text{ aryl}}$).

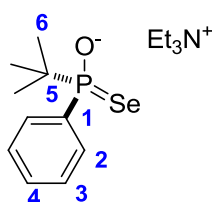
$^1\text{H NMR}$ ($CDCl_3$, 400 MHz) δ 7.83 (dd, $J = 11.6, 7.4$ Hz, 2H, H-**2**), 7.47-7.31 (m, 3H, H-**4**+H-**3**), 1.13 (d, $J = 17.9$ Hz, 9H, H-**6**).

$^{13}\text{C NMR}$ ($CDCl_3$, 101 MHz) δ 132.7 (d, $J = 10.2$ Hz, C-**2**), 132.0 (C-**1**), 131.7 (d, $J = 2.8$ Hz, C-**4**), 127.9 (d, $J = 12.2$ Hz, C-**3**), 37.6 (d, $J = 61.4$ Hz, C-**5**), 24.8 (C-**6**).

$^{31}\text{P NMR}$ ($CDCl_3$, 162 MHz) δ 97.3 (sidebands $J = 736.6$ Hz).

HRMS (ES+) calcd for $(C_{10}H_{15}OPSe + Na)^+$: 284.9918; **found**: 284.9917.

(±)-*tert*-butyl(phenyl)phosphinoselenoate

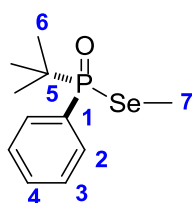


$^1\text{H NMR}$ ($CDCl_3$, 400 MHz) δ 8.02-7.93 (m, 2H, H-**2**), 7.36-7.29 (m, 3H, H-**3**+H-**4**), 1.10 (d, $J = 16.2$ Hz, 9H, H-**6**).

$^{31}\text{P NMR}$ ($CDCl_3$, 162 MHz) δ 76.0 (sidebands $J = 637.7$ Hz).

$C_{10}H_{14}OPSe^-$
 $260,2 \text{ g}\cdot\text{mol}^{-1}$

(±)-Se-methyl *tert*-butyl(phenyl)phosphinoselenoate **m41**



C₁₁H₁₇OPSe
275,2 g.mol⁻¹
Yellow oil
45%

t-BuPhP(O)H **m3** (100 mg, 0.552 mmol, 1 equiv.) was introduced as a solution in CDCl₃ (11 mL). Elemental selenium (166 mg, 2.10 mmol, 3.8 equiv.) was added as a powder, followed by trimethylamine (77 μL, 0.552 mmol, 1 equiv.). The reaction mixture was heated to 62°C and let stirring at this temperature for 15 h. MeI (35 μL, 0.552 mmol, 1 equiv.) was added at room temperature, and the reaction mixture was let stirring at this temperature for 30 minutes. The reaction was quenched by the slow addition of a diluted aqueous solution of hydrochloric acid (C = 1M). The aqueous layer was

extracted with dichloromethane (3x). The combined organic layers were washed with brine (1x), dried over MgSO₄, filtered in a glass frit and concentrated under vacuum to afford a yellow oil (65 mg, 0.247, 45%) as a crude product which was not further purified.

IR (neat): ν = 2959, 2930, 2901, 2866 ($\nu_{\text{C-H alkyl}}$), 1588, 1572, 1475, 1460 ($\nu_{\text{C=C Ar}}$), 1436 ($\delta_{\text{C-H alkyl}}$), 750, 696 ($\delta_{\text{C-H Ar}}$).

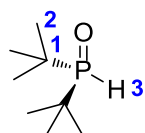
¹H NMR (CDCl₃, 400 MHz) δ 7.91-7.80 (m, 2H, H-2), 7.54-7.39 (m, 3H, H-3+H-4), 2.00 (d, J = 9.2 Hz, 3H, H-7), 1.16 (d, J = 17.5 Hz, 9H, H-6).

¹³C NMR (CDCl₃, 101 MHz) δ 132.7 (d, J = 9.4 Hz, C-2), 132.0 (d, J = 3.0 Hz, C-4), 131.5 (d, J = 81.5 Hz, C-1), 128.3 (d, J = 11.8 Hz, C-3), 37.8 (d, J = 62.9 Hz, C-5), 24.8 (d, J = 0.9 Hz, C-6), 2.2 (d, J = 3.1 Hz, C-7).

³¹P NMR (CDCl₃, 162 MHz) δ 68.4 (sidebands J = 389.8 Hz).

HRMS (ES+) calcd for (C₁₁H₁₇OPSe + Na)⁺: 575.0261; **found**: 575.0273.

di-*tert*-butylphosphine oxide **m1**



C₈H₁₉OP
162,2 g.mol⁻¹
White solid
Quant.

To 20 mL of diethylether cooled at -40°C, *t*-BuLi (1.62 M in pentane, 4.2 mL, 6.8 mmol, 3.2 equiv.) was added dropwise. To the solution obtained, diphenylphosphite (0.4 mL, 2.13 mmol, 1.0 equiv.) was added dropwise at -40°C as a solution in diethylether (5 mL). The reaction mixture was let stirring at this temperature for 1 more hour, then at room temperature for 2 days. A pale yellow solution was obtained, which was quenched by the dropwise addition of a 1 M aqueous solution of hydrochloric acid (20 mL). The aqueous phase was extracted with dichloromethane (2 x 20 mL) and chloroform (20 mL). Then the combined organic layers were

washed with brine (80 mL), dried over Na₂SO₄, filtered in a glass frit and concentrated under vacuum to give the crude product as a yellow oil. Purification by flash chromatography (Et₂O/MeOH, 95:5) afforded the pure product (345 mg, 2.13 mmol, quant.) as a white solid.

R_f = 0.23 (Et₂O/MeOH, 95:5).

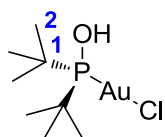
Mp: 116°C.

IR (neat): ν = 2947, 2901, 2867 ($\nu_{\text{C-H alkyl}}$), 1396, 1370 ($\delta_{\text{C-H tert-butyl}}$), 1154 ($\nu_{\text{P=O}}$).

¹H NMR (CDCl₃, 400 MHz) δ 5.80 (d, J = 425.9 Hz, 1H, H-3), 1.01 (d, J = 15.0 Hz, 18H, H-2).

¹³C NMR (CDCl₃, 101 MHz) δ 33.4 (d, J = 59.0 Hz, C-1), 25.4 (d, J = 1.6 Hz, C-2).

³¹P NMR (CDCl₃, 162 MHz) δ 66.0.



m4

C₈H₁₉AuClOP
394,6 g.mol⁻¹
Sandy powder
31%

t-Bu₂P(O)H **m1** (140 mg, 0.864 mmol, 1.0 equiv.) was introduced as a solution in dichloromethane (4 x 1 mL). Then the volume of dichloromethane was completed to 21.6 mL via syringe. ClAu.SMe₂ (255 mg, 0.864 mmol, 1.0 equiv.) was added. The reaction mixture was let stirring at reflux under an argon atmosphere for 2 hours during which the solution turned dark yellow then orange. Concentration under vacuum afforded a powder with a sand colour which was then redissolved into a minimum of dichloromethane (3 mL), and cyclohexane (30 mL) was added. The flask was placed in the fridge for 1 day and a half to make the starting phosphine oxide crystallizing. After Büchner filtration of the phosphine oxide, the complex was obtained in the filtrate as a mixture with remaining ClAu.SMe₂. This mixture was re-dissolved in 3 mL of dichloromethane, and further addition of 30 mL of cyclohexane made ClAu.SMe₂ precipitating. Second Büchner filtration allowed to completely remove ClAu.SMe₂ and afforded the pure complex as a powder with a sand colour (106 mg, 0.269 mmol, 31%).

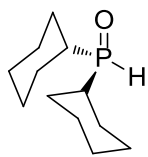
IR (neat): ν = 3134(ν_{OH}), 2954, 2868 ($\nu_{\text{C-H alkyl}}$), 1472 ($\nu_{\text{C=C aryl}}$), 1394, 1370 ($\delta_{\text{C-H tert-butyl}}$).

¹H NMR (CDCl₃, 300 MHz) δ 1.32 (d, J = 16.0 Hz, 1H, H-2).

¹³C NMR (CDCl₃, 75 MHz) δ 37.9 (d, J = 35.5 Hz, C-1), 27.5 (d, J = 6.3 Hz, C-2).

³¹P NMR (CDCl₃, 162 MHz) δ 133.1.

Dicyclohexylphosphine oxide **m2**



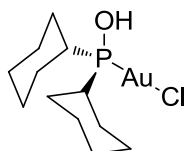
$C_{12}H_{23}OP$
214,3 g.mol⁻¹
Colorless oil
65%

Magnesium turnings (1.3 g, 54.2 mmol, 5.0 equiv.) were introduced and let stirring under an argon atmosphere. A few drops of cyclohexyl bromide and dibromoethane were introduced and the reaction mixture was heated by mean of a heat-gun in order to make the reaction starting. A grey heterogeneous bubbling solution was obtained, to which THF (43 mL) was added. Then the volume of cyclohexyl bromide was completed dropwise (6.8 mL, 54.2 mmol, 5.0 equiv.). The reaction mixture was heated to reflux for 3 hours. A dark grey solution with a suspension of white particules into it was obtained. Magnesium partially disappeared. Diphenylphosphite (2.1 mL, 10.8 mmol, 1.0 equiv.) was added dropwise at 0°C as a solution in THF (10 mL). The reaction mixture became white. It was let stirring at room temperature for 24 hours. The completion of the reaction was monitored by TLC (Et₂O/MeOH, 96:4). The reaction was quenched by the addition of a 1 M aqueous solution of hydrochloric acid (40 mL), then diluted with diethylether (30 mL). There aqueous layer was extracted with diethylether (3 x 40 mL). Then the combined organic layers were washed with a saturated aqueous solution of NaHCO₃ (120 mL), dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to give a light orange oil as the crude product. Purification by flash chromatography (Et₂O/MeOH, 97:3) afforded a colorless oil as the pure product (1.5 g, 7.08 mmol, 65%).

¹H NMR (CDCl₃, 400 MHz) δ 6.27 (d, *J* = 434.1 Hz, 1H), 2.13 – 1.88 (m, 2H), 1.88 – 1.54 (m, 4H), 1.54 – 1.33 (m, 9H), 1.33 – 0.99 (m, 7H).

¹³C NMR (CDCl₃, 101 MHz) δ 34.9 (d, *J* = 64.6 Hz), 26.2 (d, *J* = 25.6 Hz), 26.2, 26.1, 25.8 (d, *J* = 1.2 Hz), 25.0 (d, *J* = 3.5 Hz).

³¹P NMR (CDCl₃, 162 MHz) δ 50.0.



m5

$C_{12}H_{23}AuClOP$
446,7 g.mol⁻¹
Grey powder
44%

Cy₂P(O)H **m2** (103 mg, 0.481 mmol, 1.0 equiv.) was introduced as a solution in dichloromethane (6 x 1 mL). Then the volume of dichloromethane was completed to 12 mL via syringe. ClAu.SMe₂ (142 mg, 0.481 mmol, 1.0 equiv.) was added. The reaction mixture was let stirring at reflux under an argon atmosphere for 2 hours during which the starting light yellow solution turned pink then light brown. Concentration under vacuum afforded a grey powder as the pure product (95 mg, 0.213 mmol, 44%).

Mp: 224°C.

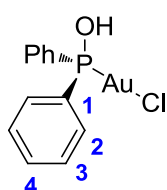
IR (neat): $\nu = 3136(\nu_{\text{OH}})$, 2927, 2852 ($\nu_{\text{C-H alkyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 6.76 (bs, 1H), 2.06 – 1.79 (m, 10H), 1.79 – 1.63 (m, 2H), 1.59 – 1.39 (m, 4H), 1.39 – 1.14 (m, 6H).

$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ 38.0 (d, $J = 43.1$ Hz), 27.7 (d, $J = 4.7$ Hz), 26.8 (d, $J = 2.0$ Hz), 26.4 (d, $J = 9.4$ Hz), 26.2 (d, $J = 5.9$ Hz), 25.9 (d, $J = 1.7$ Hz).

$^{31}\text{P NMR}$ (CDCl_3 , 162 MHz) δ 118.5.

HRMS (ES-) calcd for $(\text{C}_{12}\text{H}_{23}\text{AuClOP} - \text{H})^-$: 445.07678; found: 445.7670.



m7

$\text{C}_{12}\text{H}_{11}\text{AuClOP}$
434,6 g.mol $^{-1}$

White foam
Quant.

After Büchner filtration, the complex **m7** was obtained pure as a white foam and dried further under vacuum (261 mg; 0.60 mmol; quant.).

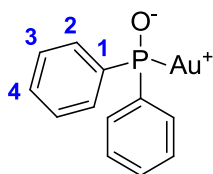
Mp: 132°C.

IR (neat): $\nu = 3056$ (ν_{OH}), 1588, 1481, 1436 ($\nu_{\text{C=CAr}}$), 746, 702 ($\delta_{2\text{ contiguous C-H Ar}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.72 – 7.61 (m, 4H, H-2), 7.53 – 7.44 (m, 2H, H-4), 7.44 – 7.33 (m, 4H, H-3).

$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ 134.4 (d, $J = 74.6$ Hz, C-1), 132.4 (d, $J = 2.7$ Hz, C-4), 131.6 (d, $J = 15.9$ Hz, C-2), 129.1 (d, $J = 12.8$ Hz, C-3).

$^{31}\text{P NMR}$ (CDCl_3 , 162 MHz) δ 89.9.



m38

$\text{C}_{12}\text{H}_{10}\text{AuOP}$
398,1 g.mol $^{-1}$
Brown powder
64%

$\text{Ph}_2\text{P(OH)AuCl}$ **m7** (568 mg, 1.31 mmol, 1 equiv.) was dissolved in CH_3CN (26.2 mL) so that a colorless heterogeneous solution was obtained.

At room temperature, the phosphazene base (0.38 mL, 1.31 mmol, 1 equiv.) was added. Then, the reaction mixture was stirred in the dark at room temperature for 30 minutes. A black homogeneous solution was obtained, to which AgSbF_6 (459 mg, 1.31 mmol, 1 equiv.) was added. A white precipitate was formed. The reaction mixture was stirred in the dark at

room temperature for 15 minutes more before the resulting brown heterogeneous mixture was filtered to give a residue that was re-dissolved in dichloromethane and filtered to give a brown powder (379 mg, 0.952 mmol, 64%) the pure product.

Mp >250°C° (degradation over 150°C).

IR (neat): $\tilde{\nu}$ = 3042 ($\nu_{\text{C-H Ar}}$), 752, 699 ($\delta_{\text{C-H Ar}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.78-7.68 (m, 2H, H-2), 7.43-7.36 (m, 3H, H-3+H-4).

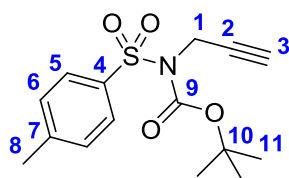
$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) ?

$^{31}\text{P NMR}$ (CDCl_3 , 162 MHz) δ 86.2 ($\text{Ph}_2\text{P}(\text{O}^-)\text{AuCl}$: δ 62.9).

HRMS (ESI) calcd for $([\text{C}_{12}\text{H}_{10}\text{OAU} + \text{Na}]^+)$: 421.0027; found: 421.0016.

tert-butyl prop-2-yn-1-yl(tosyl)carbamate

Mp = 94°C.



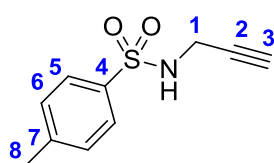
$\text{C}_{15}\text{H}_{19}\text{NO}_4\text{S}$
309,4 g.mol $^{-1}$

IR (neat): ν = 3280 ($\nu_{\text{C-H alkynyl}}$), 2982, 2933 ($\nu_{\text{C-H alkyl}}$), 2127 ($\nu_{\text{C}\equiv\text{C alkynyl}}$), 1728 ($\nu_{\text{C=O}}$), 1597, 1495 ($\nu_{\text{C=C Ar}}$), 1476 ($\delta_{\text{C-H alkyl}}$), 1456 ($\nu_{\text{C=C Ar}}$), 1353, 1151 ($\nu_{\text{S=O sulfone}}$), 845 (δ_2 contiguous C-H Ar), 637 ($\delta_{\text{C-H alkynyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.91 (d, J = 8.4 Hz, 2H, H-5), 7.31 (d, J = 8.6 Hz, 2H, H-6), 4.63 (d, J = 2.4 Hz, 2H, H-1).

$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ 150.2 (C-9), 144.5 (C-4), 136.7 (C-7), 129.3 (C-5), 128.3 (C-6), 85.0 (C-10), 79.0 (C-2), 72.2 (C-3), 35.7 (C-1), 27.9 (C-11), 21.7 (C-8).

4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide



$\text{C}_{10}\text{H}_{11}\text{NO}_2\text{S}$
209,3 g.mol $^{-1}$
White powder
90%

p-Ts(Boc)NH (4.6g, 17.0 mmol, 1.0 equiv.) was added to a suspension of K_2CO_3 (3.8 g, 27.2 mmol, 1.6 equiv.) in DMF (18.1 mL). Then the reaction mixture was let stirring at room temperature for 1 hour. Propargyl bromide (2 mL, 17.0 mmol, 1.0 equiv.) was added, and the reaction mixture was let stirring at room temperature for 2 additional hours. Completion of the reaction was monitored by TLC (Pent/Et $_2$ O, 6:4). The reaction mixture was diluted with diethyl ether (20 mL) and then, quenched by the addition of distilled water (40 mL). The aqueous layer was extracted with diethylether (3 x 40 mL). Then the combined organic layers were dried over MgSO_4 , filtered in a frit and concentrated under vacuum to give a yellow solid as the crude product. The latter was re-dissolved in dichloromethane (3.7 mL). Then trifluoroacetic acid was

added (5.6 mL) and the reaction mixture was let stirring at room temperature for 24 hours. A light brown homogeneous solution was obtained. The completion of the reaction was monitored by TLC (Pent/Et₂O, 7:3). Purification by flash chromatography (Pent/Et₂O, 5.5:4.5) afforded the pure product as a white powder (3.2 g, 15.3 mmol, 90%).

$R_f = 0.31$ (Pentane/Et₂O, 5.5:4.5).

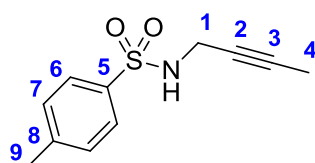
Mp: 78°C.

IR (neat): $\nu = 3267$ ($\nu_{\text{C-H alkyl}}$), 2125 ($\nu_{\text{C}\equiv\text{C alkynes}}$), 1598, 1475, 1431 ($\nu_{\text{C=C aryl}}$), 1323, 1156 ($\nu_{\text{S=O}}$), 1094, 1069 ($\delta_{\text{N-H}}$), 663 ($\delta_{\text{C-H alkynes}}$).

¹H NMR (CDCl₃, 400 MHz) δ 7.81 – 7.73 (m, 2H, H-5), 7.31 (dt, $J = 7.9, 0.8$ Hz, 2H, H-6), 4.77 – 4.54 (m, 1H, NH), 3.83 (dd, $J = 6.1, 2.5$ Hz, 2H, H-1), 2.43 (s, 3H, H-8), 2.10 (t, $J = 2.5$ Hz, 1H, H-3).

¹³C NMR (CDCl₃, 101 MHz) δ 144.0 (C-7), 136.7 (C-4), 129.9 (C-6), 127.5 (C-5), 78.1 (C-2), 73.1 (C-3), 33.0 (C-1), 21.7 (C-14).

***N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide**



C₁₁H₁₃NO₂S
223,3 g.mol⁻¹
White powder
92%

Purification by flash chromatography (Pent/Et₂O, 5.5:4.5) afforded the pure product a white powder (3.5 g, 15.7 mmol, 92%).

$R_f = 0.31$ (Pentane/Et₂O, 5.5:4.5).

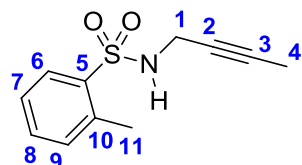
Mp: 80°C.

IR (neat): $\nu = 3265$ ($\nu_{\text{C-H alkyl}}$), 2243 ($\nu_{\text{C}\equiv\text{C alkynes}}$), 1598, 1494, 1435 ($\nu_{\text{C=C aryl}}$), 1323, 1158 ($\nu_{\text{S=O sulfone}}$), 1093, 1052 ($\delta_{\text{C-N alkyl amine}}$), 663 ($\delta_{\text{C-H alkynes}}$).

¹H NMR (CDCl₃, 400 MHz) δ 7.80 – 7.74 (m, 2H, H-6), 7.34 – 7.28 (m, 2H, H-7), 4.56 (t, $J = 5.9$ Hz, 1H, NH), 3.76 (dq, $J = 6.0, 2.4$ Hz, 2H, H-1), 2.43 (s, 3H, H-9), 1.60 (t, $J = 2.4$ Hz, 3H, H-4).

^{13}C NMR (CDCl_3 , 101 MHz) δ 143.7 (C-8), 137.0 (C-5), 129.7 (C-7), 127.6 (C-6), 81.2 (C-2), 73.4 (C-3), 33.6 (C-1), 21.7 (C-9), 3.4 (C-4).

2-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide



Mp = 55°C.

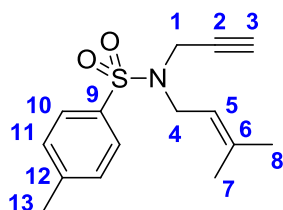
IR (neat): ν = 3296 ($\nu_{\text{N-H}}$ secondary amine), 2921 ($\nu_{\text{C-H}}$ alkyl), 2238 ($\nu_{\text{C}\equiv\text{C}}$ alkyne), 1596, 1500, 1450 ($\nu_{\text{C}=\text{C}}$ Ar), 1430 ($\delta_{\text{C-H}}$ alkyl), 1318 ($\nu_{\text{S}=\text{O}}$ sulfone), 1201 ($\nu_{\text{C-N}}$ alkyl amine), 1157 ($\nu_{\text{S}=\text{O}}$ sulfone), 1132, 1065 ($\nu_{\text{C-N}}$ alkyl amine), 759 ($\delta_{\text{C-H}}$ Ar).

$\text{C}_{11}\text{H}_{13}\text{NO}_2\text{S}$
223,3 g.mol $^{-1}$

^1H NMR (CDCl_3 , 400 MHz) δ 8.03-7.96 (m, 1H, H-6), 7.46 (td, J = 7.4 Hz, 1.3 Hz, 1H, H-8), 7.33 (t, J = 7.2 Hz, 2H, H-7+H-9), 4.61 (bs, 1H, N-H), 3.76 (q, J = 2.4 Hz, 2H, H-1), 2.67 (s, 3H, H-11), 1.60 (t, J = 2.4 Hz, 3H, H-4).

^{13}C NMR (100 MHz, CDCl_3) δ 137.7 (C-11), 137.0 (C-5), 132.5 (C-8), 132.1 (C-7), 129.2 (C-6), 125.7 (C-9), 80.4 (C-3), 73.0 (C-2), 32.6 (C-1), 19.9 (C-11), 2.8 (C-4).

4-methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide m12



$\text{C}_{15}\text{H}_{19}\text{NO}_2\text{S}$
277,4 g.mol $^{-1}$
White crystals
74%

PPh_3 (1.9 g, 7.18 mmol, 1.0 equiv.) was introduced, followed by allylic alcohol (0.75 mL; 7.18 mmol; 1.0 equiv.) and propargyltosylamine (1.5 g, 7.18 mmol, 1.0 equiv.), both in a few millilitres of THF. Then the volume of THF was completed to 67.7 mL *via* syringe. A pale yellow solution was obtained. DIAD (1.5 mL, 7.18 mmol, 1.0 equiv.) was added to it. A bright yellow solution was obtained following to this addition, which was let stirring at room temperature overnight. Completion of the reaction was monitored by

TLC (Pent/Et₂O, 1:1). The reaction mixture was concentrated under vacuum to yield a thick yellow oil as the crude product. The pure product (1.5 g, 5.42 mmol, 74%) was obtained after purification by flash chromatography (Pent/Et₂O, 8.5:1.5) as white crystals.

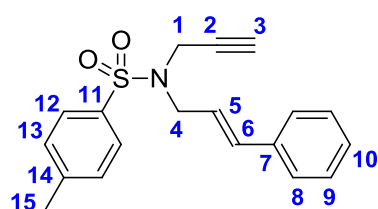
R_f = 0.33 (Pentane/Et₂O, 8.5:1.5).

Mp: 72°C.

IR (neat): ν = 3268 ($\nu_{\text{C-H alkynes}}$), 2972, 2917, 2858 ($\nu_{\text{C-H alkyl}}$), 2119 ($\nu_{\text{C}\equiv\text{C alkynes}}$), 1673 ($\nu_{\text{C}=\text{C}}$), 1598, 1494, 1452 ($\nu_{\text{C}=\text{C aryl}}$), 1346, 1159 ($\nu_{\text{S}=\text{O sulfone}}$), 658 ($\delta_{\text{C-H alkynes}}$).

¹H NMR (CDCl₃, 400 MHz) δ 7.74 (d, 2H, H-10), 7.29 (d, 2H, H-11), 5.10 (tdq, J = 7.3, 2.9, 1.5 Hz, 1H, H-5), 4.06 (d, J = 2.5 Hz, 2H, H-1), 3.81 (d, J = 7.3 Hz, 2H, H-4), 2.42 (s, 3H, H-13), 1.98 (t, J = 2.5 Hz, 1H, H-3), 1.72 (d, J = 1.2 Hz, 3H, H-8), 1.67 (d, J = 1.3 Hz, 3H, H-7).

¹³C NMR (CDCl₃, 101 MHz) δ 143.5 (C-5), 139.1 (C-6), 136.3 (C-9), 129.5 (C-11), 127.9 (C-10), 118.1 (C-2), 73.5 (C-3), 44.1 (C-4), 35.6 (C-1), 26.0 (C-8), 21.7 (C-13), 18.0 (C-7).



C₁₉H₁₉NO₂S
325,4 g.mol⁻¹

N-cinnamyl-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide

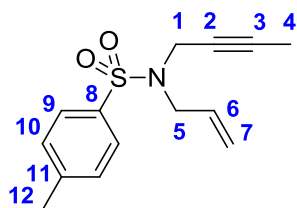
m21

IR (neat): ν = 3268 ($\nu_{\text{C-H alkynes}}$), 2923, 2855 ($\nu_{\text{C-H alkyl}}$), 2120 ($\nu_{\text{C}\equiv\text{C alkynes}}$), 1670 ($\nu_{\text{C}=\text{C}}$), 1598, 1577, 1495, 1448 ($\nu_{\text{C}=\text{C aryl}}$), 1427 ($\delta_{\text{C-H alkyl}}$), 1347, 1305, 1291 ($\delta_{\text{C-H vinyl}}$), 1160 ($\nu_{\text{S}=\text{O sulfone}}$), 969 ($\delta_{\text{C-H vinyl}}$), 844 ($\delta_{\text{C-H Ar}}$), 634 ($\delta_{\text{C-H alkynes}}$).

¹H NMR (400 MHz, CDCl₃) δ 7.80-7.74 (m, 2H, H-12), 7.38-7.22 (m, 7H, H-8 +H-9 +H-10+H-13), 6.58 (d, J = 15.8, 1H, H-6), 6.08 (dt, J = 15.8, 6.9 Hz, 1H, H-5), 4.13 (d, J = 2.4 Hz, 2H, H-1), 4.00 (dd, J = 6.9, 1.1 Hz, 2H, H-4), 2.44 (s, 3H, H-15), 2.05 (t, J = 2.5 Hz, 1H, H-3).

¹³C NMR (101 MHz, CDCl₃) δ 143.7 (C-14), 136.3 (C-11+C-7), 135.1 (C-5), 129.7 (C-13), 128.8 (C-9), 128.2 (C-10), 127.9 (C-12), 126.7 (C-8), 123.1 (C-6), 76.8 (C-2), 73.9 (C-3), 48.7 (C-4), 36.0 (C-1), 21.7 (C-15).

N-allyl-N-(but-2-yn-1-yl)-4-methylbenzenesulfonamide m18



$C_{14}H_{17}NO_2S$

263,4 g.mol⁻¹

White crystals

95%

The pure product (1.8 g, 6.84 mmol, 95%) was obtained after purification by flash chromatography (Pent/Et₂O, 9:1) as white crystals.

$R_f = 0.33$ (Pentane/Et₂O, 9:1).

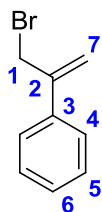
Mp: 40°C.

IR (neat): $\nu = 2921, 2854$ ($\nu_{C-H \text{ alkyl}}$), 2222 ($\nu_{C\equiv C}$), 1643 ($\nu_{C=C \text{ monosubstituted}}$), $1598, 1494, 1444$ ($\nu_{C=C \text{ aryl}}$), $1347, 1160$ ($\nu_{S=O \text{ sulfone}}$).

¹H NMR (CDCl₃, 400 MHz) δ 7.72 (d, 2H, H-9), 7.28 (d, 2H, H-10), 5.71 (ddt, $J = 17.1, 10.0, 6.4$ Hz, 1H, H-6), 5.28 – 5.15 (m, 2H, H-7), 4.00 (q, $J = 2.4$ Hz, 2H, H-1), 3.78 (dt, $J = 6.4, 1.3$ Hz, 2H, H-5), 2.41 (s, 3H, H-12), 1.53 (t, $J = 2.4$ Hz, 3H, H-4).

¹³C NMR (CDCl₃, 101 MHz) δ 143.3 (C-11), 136.3 (C-8), 132.3 (C-6), 129.3 (C-10), 127.9 (C-9), 119.6 (C-7), 81.6 (C-3), 71.7 (C-2), 49.1 (C-5), 36.4 (C-1), 21.6 (C-12), 3.3 (C-4).

(3-bromoprop-1-en-2-yl)benzene



C_9H_9Br

197,1 g.mol⁻¹

Pale yellow oil

33%

To a stirred solution of the starting material (2.4 mL, 18.3 mmol, 1 equiv.) in CHCl₃ (2.9 mL), *N*-bromosuccinimide (3.8 g, 21.0 mmol, 1.2 equiv.) was added at room temperature. A heterogeneous mixture was obtained, that was heated to reflux and let stirring at this temperature overnight. The completion of the reaction was monitored by TLC (*n*-Pent/Et₂O, 8:2). At room temperature, the reaction mixture was filtered through a short pad of silica and then was concentrated under vacuum to give a yellow oil as the crude product.

Purification by flash column chromatography on silica gel (pure pentane) afforded the pure compound as a pale yellow oil (1.2 g, 6.09 mmol, 33%).

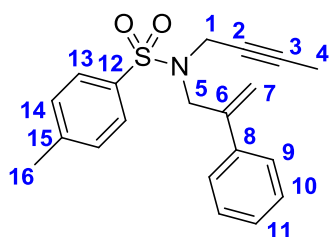
$R_f = 0.28$ (pure pentane).

IR (neat): $\nu = 1622$ ($\nu_{C=C}$), 1600, 1575, 1495, 1445 ($\nu_{C=C \text{ aryl}}$), 774, 715 ($\delta_{C-H \text{ Ar}}$).

¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.49 (m, 2H, H_{Ar}), 7.49 – 7.29 (m, 3H, H_{Ar}), 5.61 (bs, 1H, H-7), 5.53 (d, $J = 0.8$ Hz, 1H, H-7), 4.43 (d, $J = 0.8$ Hz, 2H, H-1).

¹³C NMR (100 MHz, CDCl₃) δ 144.4 (C-3), 137.8 (C-2), 128.7, 128.4, 126.3 (CH_{Ar}), 117.3 (C-7), 34.3 (C-1).

N-(but-2-yn-1-yl)-4-methyl-*N*-(2-phenylallyl)benzenesulfonamide **m8**



$C_{20}H_{21}NO_2S$
339,5 g.mol⁻¹
White powder
51%

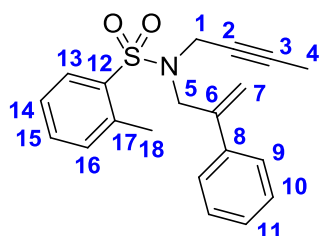
Mp = 124°C.

IR (neat): $\tilde{\nu}$ = 2920 (ν_{C-H} alkyl), 2223 ($\nu_{C\equiv C}$), 1630 ($\nu_{C=C}$), 1598, 1575, 1496, 1445 ($\nu_{C=C}$ Ar), 1379 (δ_{C-H} alkyl), 1346 ($\nu_{S=O}$), 1214, 1184 (ν_{C-N} alkyl amine), 1159 ($\nu_{S=O}$), 1092, 1064, 1029 (ν_{C-N} alkyl amine), 899 (δ_{C-H} vinyl), 815, 763, 708 (δ_{C-H} Ar).

¹H NMR (400 MHz, CDCl₃) δ 7.84-7.70 (m, 2H, H-13), 7.58-7.48 (m, 2H, H-10), 7.40-7.27 (m, 5H, H-11 + H-14 + H-9), 5.56 (s, 1H, H-7), 5.33 (q, J = 1.2 Hz, 1H, H-7), 4.23 (s, 2H, H-5), 3.93 (q, J = 2.4 Hz, 2H, H-1), 2.44 (s, 3H, H-16), 1.50 (t, J = 2.4 Hz, 3H, H-4).

¹³C NMR (100 MHz, CDCl₃) δ 143.4 (C-15), 141.7 (C-8), 138.0 (C-6), 135.9 (C-12), 129.3 (C-14), 128.5 (C-9), 128.2 (C-13 + C-11), 126.5 (C-10), 117.0 (C-7), 82.0 (C-2), 71.5 (C-3), 50.1 (C-5), 36.2 (C-1), 21.6 (C-16), 3.3 (C-4).

N-(but-2-yn-1-yl)-2-methyl-*N*-(2-phenylallyl)benzenesulfonamide



$C_{20}H_{21}NO_2S$
339,5 g.mol⁻¹
Pale yellow solid
79%

m10

Mp = 105°C.

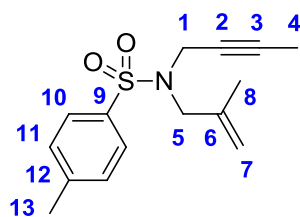
R_f = 0.33 (*n*-Pent/Et₂O, 8:2).

IR (neat): $\tilde{\nu}$ = 2920 (ν_{C-H} alkyl), 2224 ($\nu_{C\equiv C}$), 1632 ($\nu_{C=C}$), 1597, 1574, 1495, 1445 ($\nu_{C=C}$ Ar), 1324, 1157 ($\nu_{S=O}$), 1132, 1068, 1029 (ν_{C-N} alkyl amine), 895 (δ_{C-H} vinyl), 757, 708 (δ_{C-H} Ar).

¹H NMR (400 MHz, CDCl₃) δ 8.02 (dd, J = 7.9, 1.1 Hz, 1H, H-13), 7.46 (td, J = 7.5, 1.2 Hz, 1H, H-15), 7.38-7.29 (m, 1H, H-14), 7.29-7.12 (m, 7H, H_{Ar}), 5.50 (s, 1H, H-7), 5.43-5.37 (m, 1H, H-7), 4.33 (s, 2H, H-5), 3.98 (q, J = 2.1 Hz, 2H, H-1), 2.41 (s, 3H, H-18), 1.72 (t, J = 2.3 Hz, 3H, H-4).

¹³C NMR (100 MHz, CDCl₃) δ 142.3 (C-6), 13.6 (C-17), 138.4 (C-12), 137.3 (C-8), 132.9, 132.8 (CH_{Ar}), 130.4 (C-13), 128.5, 128.1, 126.4 (CH_{Ar}), 126.0 (C-14), 117.5 (C-7), 81.7 (C-3), 72.4 (C-2), 50.2 (C-5), 35.5 (C-1), 20.5 (C-18), 3.6 (C-4).

N*-(but-2-yn-1-yl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide **m39*



$C_{15}H_{19}NO_2S$
 $277,4 \text{ g}\cdot\text{mol}^{-1}$

White crystals
64%

PPh_3 (1.8 g, 6.73 mmol, 1.0 equiv.), allyl alcohol (0.58, 6.73 mmol, 1.0 equiv.) and *N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (1.5 g, 6.73 mmol, 1.0 equiv.) were introduced and dissolved in THF (65.5 mL). Then, DIAD (1.4 mL, 6.73 mmol, 1.0 equiv.) was added dropwise to the pale yellow solution so obtained, so that the solution turned light yellow. The reaction mixture was stirred at room temperature overnight. The completion of the reaction was monitored by TLC (*n*-Pent/ Et_2O , 1:1). The

reaction mixture was concentrated under vacuum to furnish a yellow oil as the crude product. The latter was then purified by flash column chromatography on silica gel (*n*-Pent/ Et_2O , 8.5:1.5) to afford the pure product as white crystals (1.2 g, 4.33 mmol, 64%).

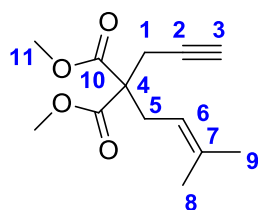
$R_f = 0.34$ (*n*-Pent/ Et_2O , 8.5:1.5).

IR (neat): $\tilde{\nu} = 3079$ (ν_{C-H} vinyl), 2975, 2920, 2855 (ν_{C-H} alkyl), 2303 ($\nu_{C\equiv C}$), 1657 ($\nu_{C=C}$), 1598, 1495, 1442 ($\nu_{C=C_{Ar}}$), 1378 (δ_{C-H} alkyl), 1349, 1330, 1306 (ν_{C-N}), 1161 ($\nu_{S=O}$), 905 (δ_{C-H} vinyl).

1H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.71 (m, 2H, H-10), 7.32-7.27 (m, 2H, H-11), 5.07-4.83 (m, 2H, H-7), 3.97 (q, $J = 2.4$ Hz, 2H, H-1), 3.70 (s, 2H, H-5), 2.42 (s, 3H, H-13), 1.76 (t, $J = 1.2$ Hz, 3H, H-8), 1.50 (t, $J = 2.4$ Hz, 3H, H-4).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.3 (C-12), 139.7 (C-6), 136.4 (C-9), 129.3 (C-11), 128.1 (C-10), 115.2 (C-7), 81.6 (C-3), 71.7 (C-2), 52.6 (C-5), 36.2 (C-1), 21.6 (C-13), 19.9 (C-8), 3.3 (C-4).

Dimethyl 2-(3-methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate **m15**



$C_{13}H_{18}O_4$
 $238,3 \text{ g}\cdot\text{mol}^{-1}$

Colorless oil

To a suspension of NaH (460 mg, 11.5 mmol, 1.3 equiv.) in DMF (12.1 mL), dimethyl propargyl malonate (1.5 g, 8.82 mmol, 1.0 equiv.) was added dropwise at $0^\circ C$. The reaction mixture was let stirring at $0^\circ C$ for 1 h. Allyl bromide (1.4 mL; 11.5 mmol; 1.3 equiv.) was then added dropwise at $0^\circ C$, and the reaction mixture was let stirring at room

temperature overnight. Completion of the reaction was monitored by TLC (Pent/Et₂O, 1:1). The reaction was quenched by the dropwise addition of a 1 M aqueous solution of hydrochloric acid (15 mL). The aqueous layer was then extracted with diethyl ether (3 x 15 mL), and the combined organic layers were washed with brine (60 mL), dried over MgSO₄, filtered in a glass frit and concentrated under vacuum to yield a heterogeneous yellow oil as the crude product. Purification by flash column chromatography on silica gel (Pent/Et₂O, 8.5:1.5) afforded the pure product (1.8 g, 7.56 mmol, 86%) as a colorless oil.

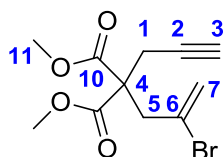
R_f = 0.33 (Pentane/Et₂O, 8.5:1.5)

IR (neat): ν = 3278 ($\nu_{\text{C-H alkynyl}}$), 2955, 2916, 2860 ($\nu_{\text{C-H alkyl}}$), 2120 ($\nu_{\text{CC alkynyl}}$), 1735 ($\nu_{\text{C=O}}$), 1674 ($\nu_{\text{C=C trisubstituted}}$).

¹H NMR (CDCl₃, 400 MHz) δ 4.88 (tp, J = 7.7, 1.4 Hz, 1H, H-6), 3.71 (s, 6H, H-11), 2.78 – 2.73 (m, 4H, H-1+H-5), 1.98 (t, J = 2.7 Hz, 1H, H-3), 1.68 (s, 3H, H-9), 1.63 (s, 3H, H-8).

¹³C NMR (CDCl₃, 101 MHz) δ 170.6 (C-10), 137.0 (C-7), 117.1 (C-6), 79.4 (C-2), 71.3 (C-3), 57.3 (C-4), 52.8 (C-11), 30.9 (C-5), 26.1 (C-9), 22.6 (C-1), 18.0 (C-8).

Dimethyl 2-(2-bromoallyl)-2-(prop-2-yn-1-yl)malonate **m20**



C₁₁H₁₃BrO₄
289,1 g.mol⁻¹
Colorless oil
Quant.

To a suspension of NaH (880 mg, 22 mmol, 1.1 equiv.) in THF (276 mL) cooled at 0°C, dimethyl propargyl malonate (3.2 mL, 20 mmol, 1 equiv.) was added dropwise. A yellow solution was obtained, that was stirred at room temperature for 15 min before the bromide derivative (2.5 mL, 24 mmol, 1.2 equiv.) was added dropwise at room temperature. The reaction mixture turned orange in colour, and then was stirred at room temperature overnight. The completion of the reaction was monitored by TLC (*n*-Pent/Et₂O, 9.5:0.5).

The reaction was quenched by the addition of a saturated aqueous solution of NH₄Cl. The aqueous layer was extracted with Et₂O and the resulting organic layer dried over MgSO₄ and concentrated under vacuum to afford the crude product as a yellow oil that was further purified by flash column chromatography on silica gel (*n*-Pent/Et₂O, 8.5:1.5). The pure compound was obtained as a colourless oil (5.8 g, 20 mmol, 1 equiv.).

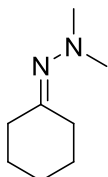
R_f = 0.31 (*n*-Pent/Et₂O, 8.5:1.5)

IR (neat): ν = 3288 ($\nu_{\text{C-H alkynyl}}$), 2954, 2844 ($\nu_{\text{C-H alkyl}}$), 2122 ($\nu_{\text{C}\equiv\text{C alkynyl}}$), 1735 ($\nu_{\text{C=O}}$), 1626 ($\nu_{\text{C=C}}$), 1435 ($\delta_{\text{C-H alkyl}}$), 1324, 1290 ($\nu_{\text{C-O}}$), 902 ($\delta_{\text{C-H vinyl}}$), 650 ($\delta_{\text{C-H alkynyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 5.83 (dt, $J = 1.6, 0.8$ Hz, 1H, H-7), 5.63 (d, $J = 1.6$ Hz, 1H, H-7), 3.76 (s, 6H, H-11), 3.30 (d, $J = 0.8$ Hz, 2H, H-5), 2.93 (d, $J = 2.7$ Hz, 2H, H-1), 2.05 (t, $J = 2.7$ Hz, 1H, H-3).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 169.6 (C-10), 126.2 (C-6), 123.0 (C-7), 78.8 (C-2), 72.2 (C-3), 56.1 (C-4), 53.2 (C-11), 43.0 (C-5), 22.4 (C-1).

2-cyclohexylidene-1,1-dimethylhydrazine



$\text{C}_8\text{H}_{16}\text{N}_2$
140,2 g.mol $^{-1}$
Yellow oil
89%

To a stirred solution of cyclohexanone (3.2 mL, 30.6 mmol, 1 equiv.) in hexane (6 mL), *N,N*-dimethylhydrazine (2.4 mL, 30.6 mmol, 1 equiv.) was added at room temperature. A heterogeneous yellow-orange solution was obtained, that was heated to reflux and let stirring at this temperature for 3.5 hours. The completion of the reaction was monitored by TLC (*n*-Pent/ Et_2O , 1:1). The reaction was quenched by water. The aqueous layer was extracted with DCM (3x). The combined organic layers were dried over MgSO_4 , filtered through a glass frit and concentrated under vacuum to afford the crude product as an orange oil. After distillation under vacuum (150°C, 35 Torr), the pure compound was obtained as a yellow oil (3.8 g, 27.1 mmol, 89%).

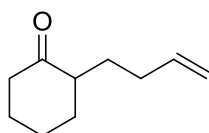
Bp: 150°C (35 Torr).

IR (neat): $\nu = 2968, 2929$ ($\nu_{\text{C-H alkyl}}$), 1655 ($\nu_{\text{C=N imine}}$), 1453 ($\delta_{\text{C-H alkyl}}$), 1407 ($\nu_{\text{C-N alkyl amine}}$), 1370 ($\delta_{\text{C-H alkyl}}$), 1151, 1072, 1019 ($\nu_{\text{C-N alkyl amine}}$).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 2.53-2.45 (m, 2H), 2.42 (s, 6H), 2.26-2.18 (m, 2H), 1.74-1.54 (m, 6H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 170.3, 47.7, 36.1, 28.8, 27.6, 26.7, 26.1.

2-(but-3-en-1-yl)cyclohexanone



$\text{C}_{10}\text{H}_{16}\text{O}$
152,2 g.mol $^{-1}$
Colorless oil
62%

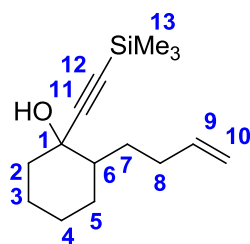
To a stirred solution of diisopropylamine (4 mL, 0.0282 mmol, 2 equiv.) in THF (16 mL) cooled at 0°C, *n*-BuLi (12.8 mL, 0.282 mmol, 2 equiv.) was added dropwise so that the solution turned to yellow. The homogeneous mixture so obtained was let stirring at room temperature for 20 min before the 2-cyclohexylidene-1,1-dimethylhydrazine (2 g, 0.0141 mmol, 1 equiv.) was added dropwise at 0°C as a solution in THF (4 x 1 mL). A brown solution was obtained, that was stirred at room temperature for 3 h. Finally, homoallyl bromide (3 mL, 0.0282

mmol, 2 equiv.) was added dropwise at 0°C and the reaction mixture was stirred at room temperature overnight. The completion of the reaction was monitored by TLC (*n*-Pent/Et₂O, 1:1). The reaction mixture was poured into a 1:1 mixture of a 2M aqueous solution of H₂SO₄ and Et₂O (64 mL) cooled to 0°C. The heterogeneous mixture so obtained was stirred at 0°C for 1 h. Then, the aqueous layer was extracted with Et₂O (3x) and the resulting combined organic layers were washed with brine (1x), dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to furnish an orange oil as the crude product. Purification by flash column chromatography on silica gel (*n*-Pent/Et₂O, 9:1 → 7.5:2.5) afforded the pure compound as a colorless oil (1.3 g, 8.54 mmol, 62%).

R_f = 0.35 (*n*-Pent/Et₂O, 1:1).

¹H NMR (400 MHz, CDCl₃) δ 5.78 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.07-4.89 (m, 2H), 2.45-2.20 (m, 3H), 2.18-1.98 (m, 4H), 1.98-1.76 (2H), 1.76-1.54 (m, 2H), 1.47-1.17 (m, 2H).

2-(but-3-en-1-yl)-1-((trimethylsilyl)ethynyl)cyclohexanol



C₁₅H₂₆OSi
250,5 g·mol⁻¹
Yellow oil
Quant.

To a stirred solution of TMSA (1.9 mL, 13.7 mmol, 1.3 equiv.) in THF (17.4 mL) cooled at -78°C, *n*-BuLi (5.3 mL, 11.6 mmol, 1.1 equiv.) was added dropwise. Then, the reaction mixture was stirred at -78°C for 30 min before a solution of 2-(but-3-en-1-yl)cyclohexanone (1.6 g, 10.5 mmol, 1 equiv.) in THF (28.8 mL) was cannulated. A yellow solution was obtained, that was stirred at -78°C for more 30 min. Then, the completion of the reaction was monitored by TLC (*n*-Pent/Et₂O, 1:1). The reaction was quenched by the addition of a saturated aqueous solution of NH₄Cl. The aqueous layer was extracted with Et₂O (3x). The combined organic layers were washed with brine (1x), dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to give a yellow oil (2.6 g, 10.5 mmol, Quant.).

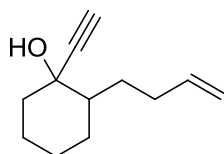
R_f = 0.74 (*n*-Pent/Et₂O, 1:1).

IR (neat): $\tilde{\nu}$ = 3444 (ν_{OH}), 2932, 2858 (ν_{C-H alkyl}), 2164 (ν_{C≡C}), 1640 (ν_{C=C}), 1446 (δ_{C-H vinyl}), 1409 (δ_{C-H vinyl}), 1361 (δ_{C-H vinyl}), 1194 (δ_{OH}), 1329 (ν_{C-O}), 994, 908 (δ_{C-H vinyl}).

¹H NMR (400 MHz, CDCl₃) δ 5.90 – 5.75 (m, 1H, H-9), 5.09 – 4.91 (m, 2H, H-10), 2.27 – 2.12 (m, 1H, H-8), 2.12 – 1.75 (m, 3H, H-2 + H-7 + H-8), 1.75 – 1.40 (m, 6H, H-2 + H-3 or H-4 or H-5), 1.40 – 1.08 (m, 2H, H-7 + H-3 or H-4 or H-5), 0.17 (s, 9H, H-13), 0.16 (s, 9H, H-13).

¹³C NMR (100 MHz, CDCl₃) δ 139.3, 139.1 (C-9), 114.6, 114.5 (C-10), 110.8, 107.4 (C-11), 90.8, 87.5 (C-12), 73.1, 70.5 (C-1), 68.1, 66.0 (C-2), 47.3, 45.0 (C-6), 41.3, 39.6 (C-3 or C-4 or C-5), 31.8, 31.7 (C-8), 29.5, 29.1 (C-7), 26.3, 25.8, 25.6, 24.2 (C-3 + C-4 + C-5), 0.2, 0.1 (C-13).

2-(but-3-en-1-yl)-1-ethynylcyclohexanol



C₁₂H₁₈O
178,3 g.mol⁻¹
Orange oil
Quant.

To a stirred solution of 2-(but-3-en-1-yl)-1-((trimethylsilyl)ethynyl)cyclohexanol (2.4 g, 9.60 mmol, 1 equiv.) in THF (20.3 mL), TBAF (10.6 mL, 10.6 mmol, 1.1 equiv.) was added dropwise at room temperature so that the solution turned from yellow to dark orange. The reaction mixture was stirred at room temperature for 1 h and the completion of the reaction was monitored by TLC (*n*-Pent/Et₂O, 1:1). The reaction was quenched by the addition of a saturated aqueous solution of

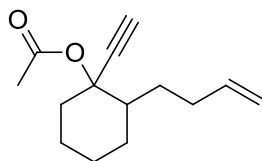
NH₄Cl. The aqueous layer was extracted with Et₂O (3x). The combined organic layers were washed with brine (1x), dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to give an orange oil (1.7 g, 9.60 mmol, Quant.).

R_f = 0.63 (*n*-Pent/Et₂O, 1:1).

IR (neat): $\tilde{\nu}$ = 3420 (ν_{OH}), 3305 (ν_{C-H alkynyl}), 2931, 2857 (ν_{C-H alkyl}), 2106 (ν_{C≡C}), 1640 (ν_{C=C}), 1446 (δ_{C-alkyl}), 1415 (δ_{C-H vinyl}), 1375 (δ_{C-H alkyl}), 1329 (ν_{C-O}), 1145 (δ_{OH}), 995, 908 (δ_{C-H vinyl}).

¹H NMR (300 MHz, CDCl₃) δ 5.81 (ddq, *J* = 17.3, 10.2, 7.2, 6.8 Hz, 1H), 5.10 – 4.89 (m, 2H), 2.47 (s, 1H), 2.43 – 1.04 (m, 12H), 0.90 (t, *J* = 7.2 Hz, 1H).

2-(but-3-en-1-yl)-1-ethynylcyclohexyl acetate m27



C₁₄H₂₀O₂
220,3 g.mol⁻¹
Colorless oil
94%

To a stirred solution of 2-(but-3-en-1-yl)-1-ethynylcyclohexanol (1.7 g, 9.60 mmol, 1 equiv.) in DCM (74 mL), DMAP (829 mg, 6.72 mmol, 70 mol%), Et₃N (4 mL, 28.8 mmol, 3 equiv.) and acetic anhydride (3.7 mL, 38.4 mmol, 4 equiv.) were successively added at room temperature. Then, the reaction mixture was heated to 40°C and stirred at this temperature overnight so that a homogeneous brownish solution was

obtained. The completion of the reaction was monitored by TLC (*n*-Pent/Et₂O, 8:2). The reaction was quenched at room temperature by distilled water. The aqueous layer was extracted with DCM (3x). The combined organic layers were washed with brine (1x), dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to afford a brown oil as the crude product. Purification by flash column chromatography on silica gel afforded the pure compound as a colourless oil (2 g, 9.13 mmol, 94%).

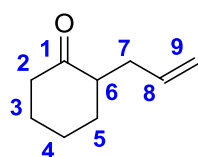
$R_f = 0.27$ (*n*-Pent/Et₂O, 9.2:0.8).

IR (neat): $\tilde{\nu} = 3289$ ($\nu_{\text{C-H alkynyl}}$), 2977, 2933, 2860 ($\nu_{\text{C-H alkyl}}$), 2114 ($\nu_{\text{C}\equiv\text{C}}$), 1743 ($\nu_{\text{C=O}}$), 1640 ($\nu_{\text{C=C}}$), 1447 ($\delta_{\text{C-H alkyl}}$), 1366 ($\delta_{\text{C-H alkyl}}$), 1314 ($\nu_{\text{C-O}}$), 1000, 908 ($\delta_{\text{C-H vinyl}}$).

¹H NMR (300 MHz, CDCl₃) δ 5.92-5.65 (m, 1H), 5.11-4.84 (m, 2H), 2.78-2.65 (m, 1H), 2.58 (s, 1H_{major}), 2.53 (s, 1H_{minor}), 2.22-2.07 (m, 1H), 2.01 (s, 3H_{minor}), 1.99 (s, 3H_{major}), 1.97-1.90 (m, 1H), 1.90-1.17 (m, 10H).

¹³C NMR (CDCl₃, 75 MHz) Major diastereomer δ 169.2, 138.9, 114.5, 79.9, 76.4 (2C), 45.2, 36.1, 31.4, 29.4, 28.2, 25.0, 23.3, 21.2; Minor diastereomer δ 169.2, 138.8, 114.6, 84.1, 81.0, 73.8, 45.2, 34.7, 31.6, 29.0, 26.0, 24.3, 22.0, 21.7.

2-allylcyclohexanone



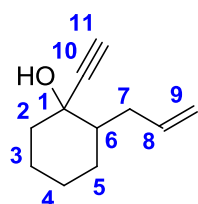
C₉H₁₄O
138,2 g.mol⁻¹

IR (neat): $\tilde{\nu} = 2932$, 2860 ($\nu_{\text{C-H alkyl}}$), 1710 ($\nu_{\text{C=O}}$), 1641 ($\nu_{\text{C=C}}$), 1449, 1362 ($\delta_{\text{C-H alkyl}}$), 1312, 1260 ($\nu_{\text{C-O}}$), 996, 914 ($\delta_{\text{C-H vinyl}}$).

¹H NMR (CDCl₃, 400 MHz) δ 5.77-5.64 (m, 2H, H-8), 5.01-4.87 (m, 4H, H-9), 2.53-2.41 (m, 1H, H-7_{dia 1}), 2.38-2.02 (m, 7H, H-6 + CH₂₁ + H-7_{dia 2}), 2.02-1.86 (m, 3H, CH₂₂ + H-7_{dia 1}), 1.85-1.73 (m, 6H, CH₂₃ + CH₂₄), 1.70-1.52 (m, 4H, CH₂₂ + CH₂₄), 1.29 (dtd, $J = 13.1, 11.9, 3.6$ Hz, 1H, H-7_{dia 2}).

¹³C NMR (CDCl₃, 100 MHz) δ 212.4, 212.0 (C-1), 136.5 (C-8), 116.2 (C-9), 50.2 (C-6), 42.0, 41.9 (CH₂₁), 33.8, 33.4 (C-7), 27.9 (CH₂₂), 27.0 (CH₂₃), 25.0 (CH₂₄).

2-allyl-1-ethynylcyclohexanol



C₁₁H₁₆O
242
164,2 g.mol⁻¹

Colorless oil
71%

To a solution of TMSA (2 mL, 14.2 mmol, 1.30 equiv.) in THF (30 mL) at -78°C, *n*-BuLi (6.7 mL, 12.0 mmol, 1.10 equiv.) was added dropwise and the

reaction mixture was stirred at -78°C for 30 minutes before 2-allylcyclohexanone (1.5 g, 10.9 mmol, 1 equiv. was introduced as a solution in THF (18 mL) *via* cannula. Then, the reaction mixture was let stirring at -78°C for 1 h. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 7:3) and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl . The aqueous layer was extracted with Et_2O (3x). Then, the combined organic layers were dried over MgSO_4 , filtered through a glass frit and concentrated under vacuum to give the crude product as a yellow oil that was further purified by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9.8:0.2 \rightarrow 9.5:0.5), and engaged as a pale yellow oil into the following step (1.0 g, 4.24 mmol, 1 equiv.). This substrate was dissolved in THF (8.5 mL), so that a clear solution was obtained, to which TBAF (4.7 mL, 4.66 mmol, 1.1 equiv.) was added dropwise at room temperature. A light yellow solution was obtained, that was let stirring at room temperature for 1 h. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 9:1) and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl . The aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over MgSO_4 , filtered through a glass frit and concentrated under vacuum to give the crude product as a yellow oil. After flash column chromatography on silica gel (*n*-Pent/EtOAc, 9.5:0.5), the pure compound was obtained as a colourless oil (490 mg, 2.99 mmol, 71%).

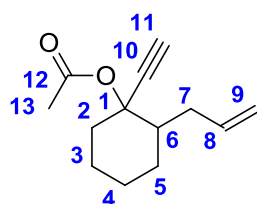
$R_f = 0.29$ (*n*-Pent/EtOAc, 9.5:0.5).

IR (neat): $\tilde{\nu} = 3400$ (ν_{OH}), 3304 ($\nu_{\text{C-H alkynyl}}$), 2975, 2932, 2857 ($\nu_{\text{C-H alkyl}}$), 2107 ($\nu_{\text{C}\equiv\text{C}}$), 1639 ($\nu_{\text{C}=\text{C}}$), 1446 ($\nu_{\text{C-H alkyl}}$), 1415 ($\delta_{\text{C-H vinyl}}$), 1352, 1326 (δ_{OH}), 1197 ($\nu_{\text{C-O}}$), 996, 910 ($\delta_{\text{C-H vinyl}}$), 630 ($\delta_{\text{C-H alkynes}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 5.87 (ddt, $J = 17.2, 10.1, 7.2$ Hz, 1H, H-8), 5.17-4.94 (m, 2H, H9), 2.61 (dddt, $J = 13.8, 6.8, 5.2, 1.3$ Hz, 1H, H-7), 2.50 (s, 1H, H-11), 2.39 (s, 1H, OH), 2.08-1.89 (m, 2H, H-7 + H-2 or H-3 or H-4 or H-5), 1.82-1.40 (m, 6H, H-6 + H-2 or H-3 or H-4 or H-5), 1.31-1.05 (m, 2H, H-2 or H-3 or H-4 or H-5).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 138.3 (C-8), 116.5 (C-9), 85.2 (C-10), 74.5 (C-11), 73.1 (C-1), 47.5 (C-6), 41.0 (C-2 or C-3 or C-4 or C-5), 36.0 (C-7), 29.5 (C-2 or C-3 or C-4 or C-5), 25.5 (C-2 or C-3 or C-4 or C-5), 24.0 (C-2 or C-3 or C-4 or C-5).

2-allyl-1-ethynylcyclohexyl acetate m48



2-allyl-1-ethynylcyclohexanol (450 mg, 2.74 mmol, 1 equiv.) was dissolved in dichloromethane (21 mL). Then, DMAP (237 mg, 1.92 mmol,

70 mol%), trimethylamine (1.1 mL, 8.22 mmol, 3 equiv.) and acetic anhydride (1.0 mL, 11.0, 4 equiv.) were successively added at room temperature. The reaction mixture was heated to reflux and stirred at this temperature overnight. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 9:1). The reaction was quenched by the addition of water. The aqueous layer was extracted with dichloromethane (3x). The combined organic layers were washed with brine (1x), dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to afford the crude product as a yellow oil. Purification by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9.8:0.2 → 9.5:0.5) yielded the pure product as a pale yellow oil (446 mg, 2.16 mmol, 79%).

$R_f = 0.11$ (*n*-Pent/EtOAc, 9.8:0.2). $R_f = 0.33$ (*n*-Pent/EtOAc, 9.5:0.5).

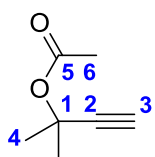
IR (neat): $\tilde{\nu} = 2935, 2861$ (ν_{C-H} alkyl), 2114 ($\nu_{C\equiv C}$), 1744 ($\nu_{C=O}$), 1641 ($\nu_{C=C}$), $1445, 1367$ (δ_{C-H} alkyl), 1267 (ν_{C-O}), 911 (δ_{C-H} vinyl), 625 (δ_{C-H} alkynyl).

¹H NMR (CDCl₃, 400 MHz) δ 5.74 (dddd, $J = 17.0, 10.1, 8.3, 5.9$ Hz, 1H, H-8), 5.11-4.86 (m, 2H, H-9), 2.79-2.68 (m, 1H, H-2), 2.61 (s, 3H, H-11), 2.58-2.49 (m, 1H, H-7), 2.00 (s, 3H, H-13), 1.98-1.85 (m, 1H, H-7), 1.81-1.42 (m, 6H, H-6 + H-5 + H-4 + H-3 + H-2), 1.36-1.07 (m, 2H, H-5 + H-4).

¹³C NMR (CDCl₃, 100 MHz) δ 169.3 (C-12), 137.2 (C-8), 116.1 (C-9), 79.7 (C-10), 76.6 (C-11), 74.0 (C-1), 45.7 (C-6), 36.2 (C-2), 35.0 (C-7), 28.1 (C-5), 25.0 (C-4), 23.4 (C-3), 22.1 (C-13).

Signals attributed to the other diastereomer: 169.2 (C-12), 137.3 (C-8), 83.9 (C-10), 80.7 (C-11), 76.7 (C-1), 45.8 (C-6), 34.7 (C-7), 25.9 (C-5), 24.3 (C-4), 21.3 (C-3), 21.7 (C-13).

2-methylbut-3-yn-2-yl acetate m23



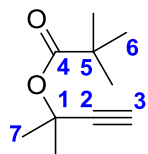
IR (neat): $\tilde{\nu} = 3282$ (ν_{C-H} alkyne), 2940 (ν_{C-H} alkyl), 2120 ($\nu_{C\equiv C}$), 1740 ($\nu_{C=O}$), $1469, 1432, 1365$ (δ_{C-H} alkyl), 646 (δ_{C-H} alkyne).

C₇H₁₀O₂
126,2 g.mol⁻¹

¹H NMR (400 MHz, CDCl₃) δ 2.53 (s, 1H, H-3), 2.03 (s, 3H, H-6), 1.67 (s, 6H, H-4).

¹³C NMR (101 MHz, CDCl₃) δ 169.5 (C-5), 84.9 (C-2), 72.3 (C-3), 71.7 (C-1), 29.0 (C-4), 22.1 (C-6).

2-methylbut-3-yn-2-yl pivalate m24



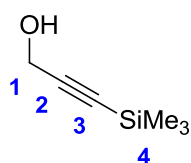
$C_{10}H_{16}O_2$
168,2 g.mol⁻¹

IR (neat): $\tilde{\nu}$ = 3307 (ν_{C-H} alkyne), 2973, 2937, 2873 (ν_{C-H} alkyl), 2254 ($\nu_{C=C}$), 1731 ($\nu_{C=O}$), 1480, 1462 (δ_{C-H} alkyl), 1398 (ν_{C-O}), 1382, 1365 (δ_{C-H} alkyl), 649 (δ_{C-H} alkyne).

¹H NMR (400 MHz, CDCl₃) δ 2.47 (s, 1H, H-3), 1.56 (s, 6H, H-7), 1.09 (s, 9H, H-6).

¹³C NMR (75 MHz, CDCl₃) δ 176.8 (C-4), 84.9 (C-2), 72.0 (C-3), 71.2 (C-1), 39.1 (C-5), 28.9 (C-7), 27.1 (C-6).

3-(trimethylsilyl)prop-2-yn-1-ol



$C_6H_{12}OSi$
128,2 g.mol⁻¹
Yellow liquid
Quant.

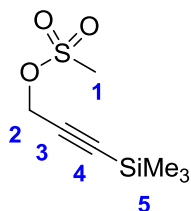
To a solution of propargyl alcohol (3 g, 53.6 mmol, 1 equiv.) in THF (67 mL) at -78°C, *n*-BuLi (51.3 mL, 123 mmol, 2.3 equiv.) was added. The reaction mixture was stirred at room temperature for 1 h. Then, TMSCl (16.0 mL, 123 mmol, 2.3 equiv.) was added at -78°C and the reaction mixture was let stirring at room temperature overnight. The reaction was quenched at 0°C by the addition of a diluted aqueous solution of HCl (C = 1M). The resulting biphasic mixture was stirred at room temperature for 1 h. Then, the aqueous layer was

extracted with Et₂O (3x) and the combined organic layers washed with a saturated aqueous solution of NaHCO₃ (1x) and brine (1x), dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to afford a yellow liquid (6.9 g, 53.6 mmol, Quant.).

¹H NMR (CDCl₃, 300 MHz) δ 4.26 (s, 2H, H-1), 0.17 (s, 9H, H-4).

¹³C NMR (100 MHz, CDCl₃) δ 104.1 (C-2), 90.5 (C-3), 51.5 (C-1), -0.1 (C-4).

3-(trimethylsilyl)prop-2-yn-1-yl methanesulfonate



$C_7H_{14}O_3SSi$
206,3 g.mol⁻¹
Yellow liquid
Quant.

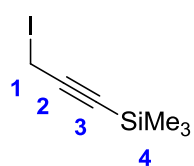
To a solution of 3-(trimethylsilyl)prop-2-yn-1-ol (2.3 mL, 15 mmol, 1 equiv.) in dichloromethane (75 mL) at 0°C, were successively added MeSO₂Cl (1.2 mL, 15.8 mmol, 1.05 equiv.) and Et₃N (2.5 mL, 18 mmol, 1.20 equiv.) and the mixture was stirred at 0°C for 1 h. A white suspension was obtained, that was let stirring further at room temperature for 30 minutes so that a colorless solution was finally obtained. After the completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 1:1), the reaction mixture was poured into ice. The aqueous layer was extracted with Et₂O (3x) and the combined organic

layers were washed with brine (1x), dried over MgSO_4 , filtered through a glass frit and concentrated under vacuum to afford a yellow oil (3.6 g, 15 mmol, Quant.).

$R_f = 0.74$ (*n*-Pent/EtOAc, 1:1).

$^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 4.84 (s, 2H, H-2), 3.12 (s, 3H, H-1), 0.20 (s, 9H, H-5).

(3-iodoprop-1-yn-1-yl)trimethylsilane



$\text{C}_6\text{H}_{11}\text{Si}$
238,1 $\text{g}\cdot\text{mol}^{-1}$
Dark red liquid
90%

NaI (4.5 g, 30 mmol, 2 equiv.) was dissolved in acetone (75 mL) so that a colorless solution was obtained. To that solution, the mesylate derivative 3-(trimethylsilyl)prop-2-yn-1-yl methanesulfonate (1.9 g, 15 mmol, 1 equiv.) was added at room temperature. An opaque yellow solution was obtained, that was stirred in dark at room temperature overnight. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 7:3). Then, the reaction mixture was filtered through a glass frit and the resulting white residue was

rinsed with Et_2O . Distillation of the filtrate under atmospheric pressure (35°C) afforded an orange liquid that was re-dissolved into Et_2O . This solution was washed with water (1x) and brine (1x). The combined aqueous layers were re-extracted with Et_2O (1x), then the combined organic layers were dried over MgSO_4 , filtered through a glass frit and concentrated under reduced pressure to yield a dark orange oil as the crude product. The latter was distilled under reduced pressure (120°C, 65 Torr) to afford the pure product as a dark red liquid (3.2 g, 13.5 mmol, 90%).

$R_f = 0.89$ (*n*-Pent/EtOAc, 7:3).

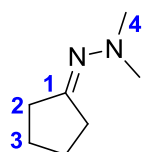
$\text{Bp} = 120^\circ\text{C}$ (65 Torr).

IR (neat): $\tilde{\nu} = 2959, 2899$ ($\nu_{\text{C-H alkyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 3.54 (s, 2H, H-1), 0.00 (s, 9H, H-4).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 102.1 (C-2), 90.9 (C-3), -0.2 (C-4), -18.1 (C-1).

2-cyclopentylidene-1,1-dimethylhydrazone



$\text{C}_7\text{H}_{14}\text{N}_2$
126,2 $\text{g}\cdot\text{mol}^{-1}$
246
Yellow oil
74%

To a solution of cyclopentanone (2.68 mL, 30 mmol, 1 equiv.) in hexane (6 mL) at 0°C, dimethylhydrazine (2.33 mL, 30 mmol, 1 equiv.) was added dropwise. The pale yellow solution so obtained was heated to 70°C and stirred at

this temperature for 4 h. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 1:1). Then, the reaction was quenched by the addition of water. The aqueous layer was extracted with Et₂O (3x) and the combined organic layers washed with brine (1x), dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to afford a dark yellow oil. The pure product was obtained after distillation under reduced pressure (95°C, 65 Torr) as a yellow oil (2.8 g, 22.2 mmol, 74%).

R_f = 0.20 (*n*-Pent/EtOAc, 1:1).

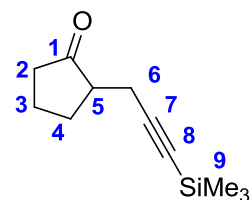
Bp = 95°C (65 Torr).

IR (neat): $\tilde{\nu}$ = 2954, 2855 ($\nu_{\text{C-H alkyl}}$), 1657 ($\nu_{\text{C=N}} + \nu_{\text{N=N}}$), 1466, 1451, 1427 ($\delta_{\text{C-H alkyl}}$), 1181, 1152, 1089, 1020 ($\nu_{\text{C-N}}$).

¹H NMR (CDCl₃, 400 MHz) δ 2.29 (s, 6H, H-4), 2.19 (dt, *J* = 18.2 Hz, 6.7 Hz, 4H, H-2), 1.65-1.48 (m, 4H, H-3).

¹³C NMR (CDCl₃, 100 MHz) δ 175.4 (C-1), 46.8 (C-4), 33.3, 29.1 (C-2), 24.7, 24.0 (C-3).

2-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclopentanone



C₁₁H₁₈OSi
194,3 g.mol⁻¹
Yellow oil
39%

To a solution of diisopropylamine (1.2 mL, 8.44 mmol, 1.1 equiv.) in THF (60 mL) at 0°C, *n*-BuLi (4.4 mL, 7.67 mmol, 1 equiv.) was added dropwise. The reaction mixture was let stirring at 0°C for 2 h so that a clear yellow solution was obtained. Then, the reaction mixture was cooled to -40°C, at which temperature 2-cyclopentylidene-1,1-dimethylhydrazone (966 mg, 7.67 mmol, 1 equiv.) was added as a solution in THF (12 mL). The reaction was stirred at 640°C for 3 h. Then, the propargyl iodide derivative (2 g, 8.44 mmol, 1.1 equiv.) was added as a solution in THF (12 mL) and the resulting mixture stirred at the same temperature overnight. The reaction was quenched by the addition of water (2 mL). Then, the reaction mixture was concentrated under vacuum to produce a brown smelly residu, that was diluted with Et₂O. The aqueous layer was extracted with Et₂O (3x) and the combined organic layers washed with water (2x), brine (1x), dried over MgSO₄, filtered through a glass frit and concentrated under vacuum to give a brown oil. The latter was stirred at room temperature in a 1:1 mixture of Et₂O and 3M aqueous solution of HCl for 1 h. The aqueous layer was then extracted with Et₂O (3x) and the combined organic layers washed with brine (1x), dried over MgSO₄, filtered through a glass frit

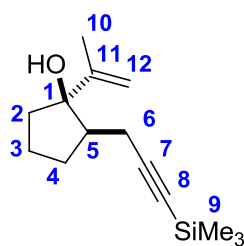
and concentrated under vacuum. A brown oil was obtained as the crude product, which was then purified by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9.5:0.5), so that the pure product was obtained as a yellow oil (579 mg, 2.98 mmol, 39%).

IR (neat): $\tilde{\nu}$ = 2961, 2899 ($\nu_{\text{C-H alkyl}}$), 2175 ($\nu_{\text{C}\equiv\text{C}}$), 1742 ($\nu_{\text{C=O}}$), 1453 ($\delta_{\text{C-H alkyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 2.53 (dd, J = 16.9, 4.0 Hz, 1H, H-6), 2.37-2.15 (m, 4H, H-5 + H-6 + 2H (H-2 or H-3 or H-4)), 2.13-1.96 (m, 2H, H-2 or H-3 or H-4), 1.84-1.66 (m, 2H, H-2 or H-3 or H-4), 0.08 (s, 9H, H-9).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 218.7 (C-1), 104.4 (C-7), 85.9 (C-8), 47.8 (C-5), 38.2, 28.7, 20.6 (C-2 + C-3 + C-4), 20.1 (C-6), 0.1 (C-9).

1-(prop-1-en-2-yl)-2-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclopentanol



$\text{C}_{14}\text{H}_{24}\text{OSi}$
236,4 $\text{g}\cdot\text{mol}^{-1}$
Colorless oil
66%

A suspension of CeCl_3 (2.5 g, 10.0 mmol, 3.9 equiv.) in THF (59 mL) was prepared and let stirring at room temperature for 1 h. Then, isopropenylmagnesium bromide (7.73 mmol, 3 equiv.) was added dropwise to the white suspension at -78°C as a solution in THF ($C = 0.5$ M). The reaction mixture was let stirring at -78°C for 2 h. Finally, 2-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclopentanone (500 mg, 2.57 mmol, 1 equiv.) was added as a solution in THF (24 mL) and the reaction mixture was slowly let warm up to room temperature overnight. The completion

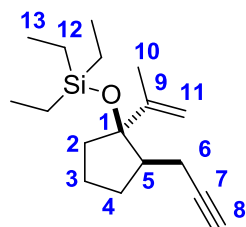
of the reaction was monitored by TLC (*n*-Pent/EtOAc, 1:1). The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl . The aqueous layer was extracted with Et_2O (3x). Then, the combined organic layers were washed with brine (1x), dried over MgSO_4 , filtered through a glass frit and concentrated under vacuum to give a yellow oil as the crude product, which was further purified by flash column chromatography on silica gel (*n*-Pent, EtOAc: 9.8:0.2 - > 9.5:0.5) so that the pure product was obtained as a colorless oil (403 mg, 1.71 mmol, 66%).

IR (neat): $\tilde{\nu}$ = 3493 (ν_{OH}), 2959, 2874 ($\nu_{\text{C-H alkyl}}$), 2173 ($\nu_{\text{C}\equiv\text{C}}$), 1641 ($\nu_{\text{C=C}}$), 1449, 1377 ($\delta_{\text{C-H}}$), 1335 ($\nu_{\text{C=O}}$), 1154 (δ_{OH}), 900 ($\delta_{\text{C-H vinyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 5.11-5.06 (m, 1H, H-12), 4.92-4.86 (m, 1H, H-12), 2.33-2.17 (m, 2H, H-6), 2.17-2.05 (m, 1H, H-5), 2.01-1.79 (m, 3H, H-2 or H-3 or H-4), 1.77 (dd, J = 1.4, 0.6 Hz, 3H, H-10), 1.71-1.55 (m, 3H, H-2 or H-3 or H-4), 0.12 (s, 9H, H-9).

¹³C NMR (CDCl₃, 100 MHz) δ 148.3 (C-11), 110.8 (C-12), 106.6 (C-7), 85.7 (C-8), 84.6 (C-1), 44.9 (C-5), 39.6, 29.6, 21.4 (C-2 + C-3 + C-4), 19.8 (C-10), 18.8 (C-6), 0.2 (C-9).

Triethyl((-1-(prop-1-en-2-yl)-2-(prop-2-yn-1-yl)cyclopentyl)oxy)silane m63



C₁₇H₃₀OSi
278,5 g.mol⁻¹
Colorless oil
45% over 2 steps

1-(prop-1-en-2-yl)-2-(3-(trimethylsilyl)prop-2-yn-1-

yl)cyclopentanol (350 mg, 1.48 mmol, 1 equiv.) was introduced as a solution in MeOH (11.4 mL). A colorless solution is obtained, to which K₂CO₃ (1.3 g, 9.47 mmol, 6.4 equiv.) was added. A pale yellow heterogeneous solution is obtained, that is let stirring at room temperature for 2 h. Then, the reaction mixture was diluted with Et₂O and the reaction was quenched by the addition of a saturated aqueous solution of NH₄Cl. The aqueous layer was extracted with Et₂O (3x). Then, the organic layers were washed with brine (1x), dried over MgSO₄, filtered

over a glass frit and concentrated under vacuum to give a yellow oil as the crude product (205 mg, 1.25 mmol, 1 equiv.). The latter was engaged directly in the following step without further purification, introduced as a solution in dichloromethane (3 mL), then 2,6-lutidine was added (1.3 mL, 11.3 mmol, 9 equiv.). At 0°C, TESOTf (0.28 mL, 1.25 mmol, 1 equiv.) was added dropwise, then the reaction mixture was let stirring at 0°C for 1.5 h. The reaction was quenched by the addition of a saturated aqueous solution of NaHCO₃. The aqueous layer was extracted with dichloromethane (3x) and the combined organic layers were washed with brine (1x), dried over MgSO₄, filtered over a glass frit and concentrated under vacuum to give a yellow liquid as the crude product. The latter was purified by flash column chromatography on silica gel (pure *n*-Pentane) to yield the pure product as a colorless oil (155 mg, 0.558 mmol, 45%).

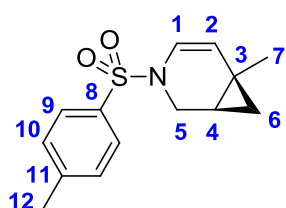
R_f = 0.61 (pure *n*-Pentane)

IR (neat): $\tilde{\nu}$ = 2954, 2912, 2876 (ν_{C-H alkyl}), 2218 (ν_{C≡C}), 1642 (ν_{C=C}), 1452 (δ_{C-H alkyl}), 901 (δ_{C-H vinyl}), 625 (δ_{C-H alkynyl}).

¹H NMR (CDCl₃, 400 MHz) δ 4.98 (dd, *J* = 2.1, 0.6 Hz, 1H, H-11), 4.86 (dq, *J* = 2.8, 1.4 Hz, 1H, H-11), 2.29 (ddd, *J* = 16.9, 3.5, 2.8 Hz, 1H, H-6), 2.16-1.83 (m, 4H, H-5 + H-8 + 2H (H-2 or H-3 or H-4)), 1.83-1.70 (m, 5H, H-10 + 2H (H-2 or H-3 or H-4)), 1.68-1.45 (m, 2H, H-2 or H-3 or H-4), 0.94 (t, *J* = 7.9 Hz, 9H, H-12), 0.60 (q, *J* = 8.1 Hz, 6H, H-13).

¹³C NMR (CDCl₃, 100 MHz) δ 147.9 (C-9), 111.6 (C-11), 86.5 (C-1), 85.3 (C-7), 67.8 (C-8), 48.1 (C-5), 37.2, 29.7, 22.0 (C-2 + C-3 + C-4), 19.9 (C-10), 17.9 (C-6), 7.4 (C-13), 6.8 (C-12).

6-methyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene **m19**



$C_{14}H_{17}NO_2S$
263,4 g.mol⁻¹
White crystals
69%

$Ph_2P(OH)AuCl$ **m7** (3 mg, 0.00380 mmol, 2 mol%) and $AgSbF_6$ (5 mg, 0.0152 mmol, 4 mol%) were introduced, then dissolved into dichloromethane (0.53 mL). A yellow solution was obtained, which was let stirring at room temperature for 5 minutes. Then the substrate **m18** (100 mg, 0.380 mmol, 1.0 equiv.) was added as a solution in dichloromethane (3 x 0.5 mL). The yellow colour disappeared. The volume of dichloromethane was completed at 6.3 mL via syringe. The solution changed in colour and became yellow again, then brown. The reaction mixture was let stirring at room temperature for 15 hours. A dark red solution was obtained. Completion of the reaction was monitored by TLC (PE/EtOAc, 80:20) and the solution was filtered over a pad of silica. The flask and silica were rinsed with a large amount of Et_2O , and the filtrate was concentrated under vacuum to afford a yellow oil as the crude product. Purification by flash chromatography (Pent/ Et_2O , 8.5:1.5 →8:2) gave white crystals as the pure product (69 mg, 0.262 mmol, 69%).

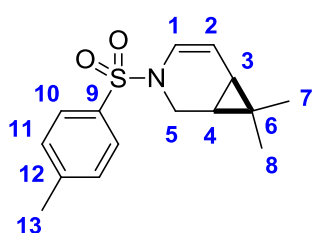
$R_f = 0.28$ (pentane/ Et_2O , 8.5:1.5).

Mp: 76°C.

IR (neat): $\nu = 2954, 2927, 2873$ (ν_{C-H} alkyl), 1647 ($\nu_{C=C}$ *cis*-disubstituted), 1599, 1496, 1451 ($\nu_{C=C}$ Ar), 1404 (ν_{N-H} aliphatic amine), 1381 (δ_{C-H} CH₃), 1346, 1165 ($\nu_{S=O}$ sulfone), 834 (δ_2 contiguous C-H Ar).

¹H NMR ($CDCl_3$, 400 MHz) δ 7.67 – 7.59 (m, 2H, H-**9**), 7.32 – 7.27 (m, 2H, H-**10**), 6.29 (dd, $J = 8.1, 1.0$ Hz, 1H, H-**1**), 5.21 (dd, $J = 8.1, 0.9$ Hz, 1H, H-**11**), 3.82 (dt, $J = 11.5, 1.3$ Hz, 1H, H-**5**), 3.03 (ddt, $J = 11.5, 2.8, 0.8$ Hz, 1H, H-**5**), 2.41 (s, 3H, H-**12**), 1.32 – 1.19 (m, 1H, H-**4**), 1.08 (s, 3H, H-**7**), 0.56 (ddd, $J = 8.5, 4.4, 0.9$ Hz, 1H, H-**6**), 0.48 – 0.40 (m, 1H, H-**6**).

¹³C NMR ($CDCl_3$, 101 MHz) δ 143.7 (C-**11**), 135.0 (C-**8**), 129.8 (C-**10**), 127.1 (C-**9**), 120.3 (C-**1**), 116.6 (C-**2**), 41.1 (C-**1**), 25.8 (C-**4**), 23.3 (C-**7**), 21.6 (C-**12**), 20.9 (C-**6**), 12.8 (C-**3**).



7,7-dimethyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene **m14**

$R_f = 0.20$ (*n*-Pent/ $EtOAc$, 9.5:0.5)

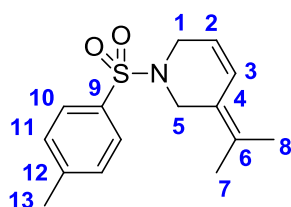
250 $C_{15}H_{19}NO_2S$
277,4 g.mol⁻¹
Orange residue
8%

IR (neat): $\nu = 2925, 2869$ ($\nu_{\text{C-H alkyl}}$), 1650 ($\nu_{\text{C=C cis-disubstituted}}$), $1599, 1495, 1457$ ($\nu_{\text{C=C Ar}}$), 1378 ($\delta_{\text{C-H CH}_3}$), $1351, 1167$ ($\nu_{\text{S=O sulfone}}$), 692 ($\delta_{\text{C-H vinyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 143.8 (C-12), 134.9 (C-9), 129.8 (C-11), 127.3 (C-10), 122.5 (C-1), 104.4 (C-2), 38.8 (C-5), 27.5 (C-7 or C-8), 25.6 (C-6), 22.0 (C-13), 21.7 (C-4), 18.9 (C-3), 14.2 (C-7 or C-8).

$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ 7.71-7.60 (m, 2H, H-10), 7.33-7.27 (m, 2H, H-11), 6.59 (d, $J = 8.4$ Hz, 1H, H-1), 5.07 (dd, $J = 8.4, 4.8$ Hz, 1H, H-2), 3.48 (dd, $J = 12.1, 1.5$ Hz, 1H, H-5), 3.37 (dd, $J = 12.2, 6.0$ Hz, 1H, H-5), 2.42 (s, 3H, H-13), 1.08-1.01 (m, 4H, H-4 + H-7 or H-8), 0.98 (dd, $J = 8.8, 4.8$ Hz, 1H, H-3), 0.74 (s, 3H, H-7 or H-8).

3-(propan-2-ylidene)-1-tosyl-1,2,3,6-tetrahydropyridine **m13**



$\text{C}_{15}\text{H}_{19}\text{NO}_2\text{S}$
277,4 $\text{g}\cdot\text{mol}^{-1}$
White crystals
58%

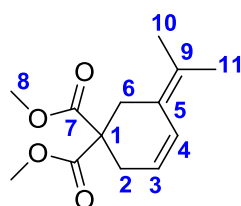
Purification by flash chromatography (Pent/ Et_2O , 8.5:1.5 \rightarrow 8:2) gave white crystals as the pure product (58 mg, 0.220 mmol, 58%). $R_f = 0.20$ (pentane/ EtOAc , 90:10).

IR (neat): $\nu = 3049$ ($\nu_{\text{C-H cis-disubstituted alkene}}$), 2922, 2857 ($\nu_{\text{C-H alkyl}}$), 1651 ($\nu_{\text{C=C cis-disubstituted alkene}}$), 1599, 1496, 1453 ($\nu_{\text{C=C Ar}}$), 1381 ($\delta_{\text{C-H CH}_3}$), 1345, 1159 ($\nu_{\text{S=O sulfone}}$).

$^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 7.57 (d, $J = 8.3$ Hz, 1H, H-10), 7.19 (d, $J = 8.3$ Hz, 1H, H-11), 6.25 (dt, $J = 10.3, 2.2$ Hz, 1H, H-3), 5.44 (dt, $J = 10.3, 3.7$ Hz, 1H, H-2), 3.86 – 3.77 (m, 2H, H-5), 3.73 – 3.63 (m, 2H, H-1), 2.32 (s, 3H, H-13), 1.68 (s, 3H, H-7 or H-8), 1.59 (s, 3H, H-7 or H-8).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 143.4 (C-12), 134.2 (C-9), 129.9 (C-6), 129.4 (C-11), 127.7 (C-10), 124.5 (C-3), 122.4 (C-4), 121.0 (C-1), 45.1 (C-5), 45.1 (C-1), 21.5 (C-13), 20.3 (C-7 or C-8), 19.7 (C-7 or C-8).

Dimethyl 5-(propan-2-ylidene)cyclohex-3-ene-1,1-dicarboxylate **m44**



$\text{C}_{13}\text{H}_{18}\text{O}_4$
238,3 $\text{g}\cdot\text{mol}^{-1}$
Experimental Part
Yellow oil
44%

The catalyst $\beta\text{-ICyDAuCl}$ (26 mg, 0.00840 mmol, 2 mol%) and AgSbF_6 (3 mg, 0.00840 mmol, 2 mol%) were introduced as solutions in dioxane (0.64 mL and 0.32 mL respectively). Then, water (0.27 mL) was added and finally, the substrate **m15** (100 mg, 0.420 mmol, 1 equiv.) was

introduced as a solution in dioxane (3 x 0.33 mL). A heterogeneous solution was obtained, that was heated to reflux and stirred at this temperature for 2.5 h. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 7:3) and the reaction mixture filtered through a short pad of silica to give the crude product as a yellow oil. The latter was purified by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9:1 -> 7:3) to afford the pure product as a yellow oil (44 mg, 0.185 mmol, 44%).

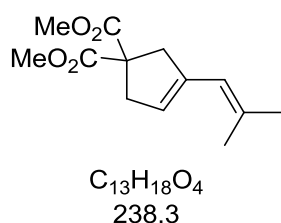
$R_f = 0.32$ (*n*-Pent/EtOAc, 9:1).

IR (neat): $\tilde{\nu} = 2953, 2914, 2860$ ($\nu_{C-H \text{ alkyl}}$), 1735 ($\nu_{C=O}$), 1643 ($\nu_{C=C}$), $1435, 1376$ ($\delta_{C-H \text{ alkyl}}$), $1346, 1312, 1299$ (ν_{C-O}).

1H NMR ($CDCl_3$, 400 MHz) δ 6.42 (dt, $J = 10.2, 2.0$ Hz, 1H, H-4), 5.60 (dt, $J = 10.4, 4.2$ Hz, 1H, H-3), 3.69 (s, 6H, H-8), 2.86-2.78 (m, 2H, H-6), 2.69 – 2.62 (m, 2H, H-2), 1.77 (s, 3H, H-10 or H-11), 1.76 (s, 3H, H-10 or H-11).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.9 (C-7), 129.8 (C-9), 125.8 (C-4), 123.9 (C-5), 122.6 (C-3), 54.2 (C-1), 52.7 (C-8), 32.2 (C-6), 31.2 (C-2), 20.6 (C-10 or C-11), 20.1 (C-10 or C-11). Spectral data are in agreement with the literature [Gryparis, C., Efe, C., Raptis, C., Lykakis, I.N., Stratakis, M., *Org. Lett.* **2012**, *14*, 2956-2959].

Dimethyl 3-(2-methylprop-1-en-1-yl)cyclopent-3-ene-1,1-dicarboxylate **m16**



$I\text{PrAuCl}$ (4.2 mg, 0.00639 mmol, 2 mol%) and AgSbF_6 (2.2 mg, 0.00639 mmol, 2 mol%) were introduced in a round bottom flask under an argon atmosphere and anhydrous CH_2Cl_2 (9.0 mL) was added. The solution was stirred at room temperature for 5 minutes, then the enyne **m15** was introduced (76 mg, 0.319 mmol, 1.0 equiv.) as a solution in CH_2Cl_2 (4 x 1 mL). The reaction mixture was stirred at room temperature for 18 h with the completion of the reaction being monitored by TLC. After completion, the solution was filtered through a pad of silica and the pad was washed with diethylether. The solvent was

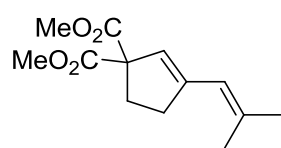
removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel (Pentane/Et₂O, 85:15) to afford a mixture of isomers in a 1:0.65 ratio (66 mg, 0.277 mmol, 88%) and as a yellow oil.

IR (neat): $\tilde{\nu}$ = 2954, 2923, 2854 ($\nu_{\text{C-H alkyl}}$), 1734 ($\nu_{\text{C=O}}$), 1654 ($\nu_{\text{C=C}}$), 1434, 1379 ($\delta_{\text{C-H alkyl}}$), 792 ($\delta_{\text{C-H vinyl}}$).

¹H NMR (CDCl₃, 400 MHz) δ 5.88 – 5.68 (m, 1H), 5.40 – 5.33 (m, 1H), 3.72 (s, 6H), 3.21 – 3.14 (m, 2H), 3.06 – 2.99 (m, 2H), 1.80 (s, 3H), 1.76 (s, 3H).

¹³C NMR (CDCl₃, 101 MHz) δ 172.7 (2C), 138.8, 135.7, 124.9, 120.8, 59.4, 52.9 (2C), 43.4, 40.4, 27.3, 19.9. Spectral data are in agreement with the literature [Hoye, T.R., Suriano, J.A. *Organometallics*. **1992**, *11*, 2044-2050].

Dimethyl 3-(2-methylprop-1-en-1-yl)cyclopent-2-ene-1,1-dicarboxylate **m17**



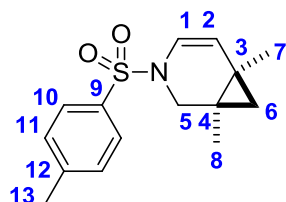
C₁₃H₁₈O₄
238,3

¹H NMR (CDCl₃, 400 MHz) δ 5.81 – 5.75 (m, 1H), 5.60 – 5.55 (m, 1H), 3.70 (s, 6H), 2.68 – 2.59 (m, 2H), 2.50 – 2.41 (m, 2H), 1.82 (s, 3H), 1.79 (s, 3H).

¹³C NMR (CDCl₃, 101 MHz) δ 172.0 (2C), 146.2, 138.1, 124.5, 120.7, 66.1, 52.7 (2C), 34.9, 32.2, 27.5, 20.0. Spectral data are in agreement

with the literature [Nieto-Oberhuber, C., Munoz, M.P., Lopez, S., Jimenez-Nunez, E., Nevado, C., Herrero-Gomez, E., Raducan, M., Echavarren, A.M. *Chem. Eur. J.* **2006**, *12*, 1677-1693].

1,6-dimethyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene **m40**



C₁₅H₁₉NO₂S
277,4 g.mol⁻¹
White powder
80%

IPrAuCl (4.5 mg, 0.007 mmol, 2 mol%) and AgSbF₆ (2.5 mg, 0.007 mmol, 2 mol%) were introduced in a round bottom flask under an argon atmosphere and anhydrous CH₂Cl₂ (14.0 mL) was added. The solution was stirred at room temperature for 5 minutes, then the enyne **m39** was introduced (97 mg, 0.350 mmol, 1.0 equiv., 0.025 M). The reaction mixture was stirred at room temperature for 3h with the completion of the reaction being monitored by TLC. After completion, the solution was filtered through a pad of silica and the pad was

washed with diethylether. The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel (Pentane/Et₂O, 8.5:1.5) to afford a white powder (78 mg, 0.282 mmol, 80%, 0% ee).

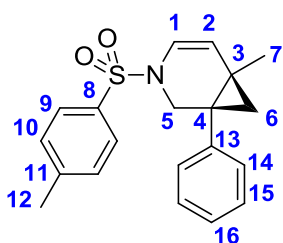
Mp = 96°C.

IR (neat): $\tilde{\nu}$ = 2924, 2873 ($\nu_{\text{C-H alkyl}}$), 1645 ($\nu_{\text{C=C}}$), 1598, 1494, 1445 ($\nu_{\text{C=C Ar}}$), 1347, 1160 ($\nu_{\text{S=O sulfone}}$), 695 ($\delta_{\text{C-H vinyl}}$), 814 ($\delta_{\text{C-H Ar}}$).

¹H NMR (CDCl₃, 400 MHz) δ 7.69 – 7.58 (m, 2H, H-**10**), 7.34 – 7.27 (m, 2H, H-**11**), 6.24 (dd, J = 8.0, 1.2 Hz, 1H, H-**1**), 5.16 (d, J = 8.0 Hz, 1H, H-**2**), 3.76 (d, J = 11.4 Hz, 1H, H-**5**), 2.66 (dd, J = 11.4, 0.9 Hz, 1H, H-**5**), 2.40 (s, 3H, H-**13**), 1.10 (s, 3H, H-**7** or H-**8**), 1.09 (s, 3H, H-**7** or H-**8**), 0.71 (d, J = 4.3 Hz, 1H, H-**6**), 0.31 (dd, J = 4.3, 1.2 Hz, 1H, H-**6**).

¹³C NMR (CDCl₃, 101 MHz) δ 143.7 (C-**12**), 135.1 (C-**9**), 129.8 (C-**11**), 127.1 (C-**10**), 120.1 (C-**1**), 118.3 (C-**2**), 46.7 (C-**5**), 29.4 (C-**4**), 26.3 (C-**6**), 21.6 (C-**13**), 18.8 (C-**7** or C-**8**), 17.7 (C-**3**), 17.6 (C-**7** or C-**8**). Spectral data are in agreement with the literature [Fürstner, A., Szillat, H., Stelzer, F. J. *Am. Chem. Soc.* **2000**, *122*, 6785-6786].

6-methyl-1-phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene **m9**



C₂₀H₂₁NO₂S
339,5 g.mol⁻¹

Mp = 123°C.

IR (neat): $\tilde{\nu}$ = 2925, 2870 ($\nu_{\text{C-H alkyl}}$), 1644 ($\nu_{\text{C=C}}$), 1598, 1494, 1446 ($\nu_{\text{C=C Ar}}$), 1349, 1162 ($\nu_{\text{S=O sulfone}}$), 764, 703 ($\delta_{\text{C-H Ar}}$), 670 ($\delta_{\text{C-H vinyl}}$).

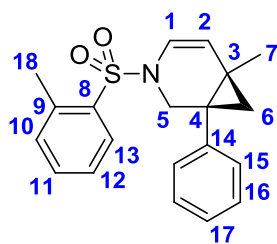
¹H NMR (CDCl₃, 400 MHz) δ 7.61-7.49 (m, 2H, H-**9**), 7.28-7.08 (m, 7H, H-**10** + H-**14** or H-**15** or H-**16**), 6.30 (dd, J = 8.0, 1.1 Hz, 1H, H-**1**), 5.27 (d, J = 8.0 Hz, 1H, H-**2**), 3.92-3.84 (m, 1H, H-**5**), 2.95-2.86 (m, 1H, H-**5**),

2.34 (s, 3H, H-12), 1.11 (d, $J = 4.6$ Hz, 1H, H-6), 0.88 (dd, $J = 4.6, 1.3$ Hz, 1H, H-6), 0.76 (s, 3H, H-7).

^{13}C NMR (CDCl_3 , 101 MHz) δ 143.8 (C-11), 139.0 (C-13), 135.0 (C-8), 129.9 (2C), 128.6, 127.3 (CH_{Ar}), 127.1 (C-9), 120.1 (C-1), 118.1 (C-2), 48.2 (C-5), 39.7 (C-4), 24.2 (C-6), 21.7 (C-12), 20.9 (C-7), 18.9 (C-3).

6-methyl-1-phenyl-3-(o-tolylsulfonyl)-3-azabicyclo[4.1.0]hept-4-ene **m11**

Mp = 129°C.



$\text{C}_{20}\text{H}_{21}\text{NO}_2\text{S}$
339,5 $\text{g}\cdot\text{mol}^{-1}$

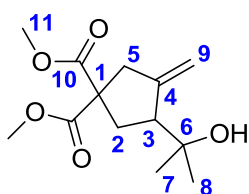
IR (neat): $\tilde{\nu} = 2926, 2870$ ($\nu_{\text{C-H alkyl}}$), 1642 ($\nu_{\text{C=C}}$), 1601, 1496, 1446 ($\nu_{\text{C=C Ar}}$), 1336, 1160 ($\nu_{\text{S=O sulfone}}$), 761, 711 ($(\delta_{\text{C-H Ar}})$), 699 ($\delta_{\text{C-H vinyl}}$).

^1H NMR (CDCl_3 , 400 MHz) δ 7.80 (dd, $J = 7.9, 1.4$ Hz, 1H, H-13), 7.36 (td, $J = 7.5, 1.4$ Hz, 1H, H-11), 7.29-7.07 (m, 7H, H_{Ar}), 6.38 (dd, $J = 8.0, 1.1$ Hz, 1H, H-1), 5.31 (d, $J = 8.0$ Hz, 1H, H-2), 3.73 (d, $J = 12$ Hz, 1H, H-5), 3.11 (dd, $J = 11.9, 1.3$ Hz, 1H, H-5), 2.52 (s, 3H, H-18), 1.10 (d, $J = 4.6$

Hz, 1H, H-6), 0.93 (dd, $J = 4.6, 1.4$ Hz, 1H, H-6), 0.79 (s, 3H, H-7).

^{13}C NMR (CDCl_3 , 100 MHz) δ 138.9 (C-14), 137.6 (C-8 or C-9), 136.8 (C-8 or C-9), 133.1 (C-11), 132.9 (CH_{Ar}), 130.0 (C-13), 129.8, 128.6, 127.3, 126.4 (CH_{Ar}), 120.9 (C-1), 117.6 (C-2), 47.9 (C-5), 40.1 (C-4), 24.6 (C-6), 21.0 (C-7), 20.9 (C-18), 19.1 (C-3).

Dimethyl 3-(2-hydroxypropan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate **m45**



$\text{C}_{13}\text{H}_{20}\text{O}_5$
256,3 $\text{g}\cdot\text{mol}^{-1}$
Yellow oil
Quant.

The catalyst IPrAuCl (6 mg, 0.00840 mmol, 2 mol%) was introduced and dissolved in dioxane (0.64 mL). AgSbF_6 (3 mg, 0.00840 mmol, 2 mol%) was added as a solution in dioxane (0.32 mL, C = 9.5 mg/L). Water (0.27 mL) was added. Then, the substrate **m15** (100 mg, 0.420 mmol, 1 equiv.) was introduced as a solution in dioxane (3 x 0.33 mL) and the white heterogeneous solution so obtained was stirred in the dark at room temperature for 14 h. The completion of the reaction was

monitored by TLC (*n*-Pent/EtOAc, 7:3). Then, the reaction mixture was filtered through a short pad of silica rinsed with EtOAc, and concentrated under vacuum to afford the crude product as a yellow oil. The latter was further purified by flash column chromatography on silica gel (*n*-Pent/EtOAc, 7:3), so that the pure compound was obtained as a yellow oil (108 mg, 0.420 mmol, Quant.).

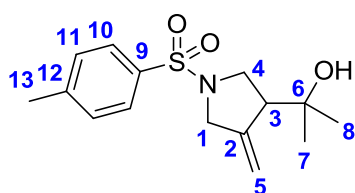
$R_f = 0.27$ (*n*-Pent/EtOAc, 7:3).

IR (neat): $\tilde{\nu} = 3525$ (ν_{OH}), 2956, 2849 ($\nu_{\text{C-H alkyl}}$), 1728 ($\nu_{\text{C=O}}$), 1656 ($\nu_{\text{C=C}}$), 1327, 1270 ($\nu_{\text{C-O}}$), 690

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 5.10-5.02 (m, 1H, H-9), 5.02-4.97 (m, 1H, H-9), 3.70 (s, 3H, H-11), 3.69 (s, 3H, H-11), 2.90-2.81 (m, 2H, H-5), 2.72-2.52 (m, 2H, H-2 + H-3), 2.00-1.94 (m, 1H, H-2), 1.21 (s, 3H, H-7 or H-8), 1.17 (s, 3H, H-7 or H-8).

$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ 172.0, 171.9 (C-10), 148.6 (C-4), 111.2 (C-9), 72.6 (C-6), 58.8 (C-1), 52.8 (C-11), 52.7 (C-3), 43.5 (C-5), 36.2 (C-2), 28.1 (C-7 or C-8), 26.2 (C-7 or C-8).

2-(4-methylene-1-tosylpyrrolidin-3-yl)propan-2-ol **m33**



$\text{C}_{15}\text{H}_{21}\text{NO}_3\text{S}$
295,4 g.mol⁻¹
Yellow oil
80%

Dioxane and distilled water were degassed under argon for 30 minutes. *t*-Bu₂P(OH)AuCl **m4** (7 mg, 0.0181 mmol, 5 mol%) and AgSbF₆ (6 mg, 0.0181 mmol, 5 mol%) were introduced, then dissolved into dioxane (0.62 mL). Instantly, a dark solution was obtained. After a 5 minute-stirring, the substrate **m12** (100 mg, 0.361 mmol, 1.0 equiv.) was introduced, followed by distilled water (0.10 mL). A purple solution was

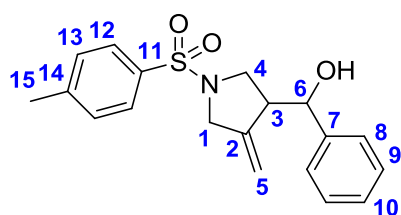
obtained, that was let stirring at 50°C under argon and protected from light. Completion of the reaction was monitored by TLC (Pent/Et₂O, 4:6). After 24 hours, the dark solution was filtered over a pad of silica. The flask and silica were rinsed with a large amount of Et₂O. Then the filtrate was concentrated under vacuum to give a yellow oil as the crude product. The latter was further purified by flash chromatography (Pent/Et₂O, 2.5:7.5). The pure product (86 mg, 0.336 mmol, 80%) was obtained as a yellow oil.

$R_f = 0.28$ (pentane/Et₂O, 2.5:7.5).

IR (neat): $\nu = 3520$ (ν_{OH} with intermolecular H-bond), 2926, 2856 ($\nu_{\text{C-H alkyl}}$), 1663 ($\nu_{\text{C=C gem-disubstituted}}$), 1600, 1464 ($\nu_{\text{C=C aryl}}$), 1379 ($\delta_{\text{C-H CH}_3}$), 1343, 1162 ($\nu_{\text{S=O sulfone}}$), 1097 (δ_{OH}).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.71 (d, $J = 8.3$ Hz, 2H, H-10), 7.33 (d, $J = 7.9$ Hz, 2H, H-11), 5.10 (dq, $J = 8.5, 2.0$ Hz, 2H, H-5), 3.88 (dtd, $J = 13.8, 2.4, 1.6$ Hz, 1H, H-1), 3.73 (dt, $J = 13.7, 2.0$ Hz, 1H, H-1), 3.43 (dd, $J = 10.2, 3.4$ Hz, 1H, H-4), 3.26 (dd, $J = 10.2, 7.8$ Hz, 1H, H-4), 2.72 – 2.61 (m, 1H, H-3), 2.43 (s, 3H, H-13), 1.18 (s, 3H, H-8 or H-9), 1.17 (s, 3H, H-8 or H-9).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 145.0 (C-2), 143.9 (C-12), 132.8 (C-9), 129.8 (C-11), 128.0 (C-10), 111.2 (C-5), 72.1 (C-6), 54.0 (C-3), 53.0 (C-1), 50.2 (C-4), 27.3 (C-7 or C-8), 27.0 (C-7 or C-8), 21.7 (C-13).



$\text{C}_{19}\text{H}_{21}\text{NO}_3\text{S}$
 343,4 $\text{g}\cdot\text{mol}^{-1}$
 Yellow oil
 60%

(4-methylene-1-tosylpyrrolidin-3-yl)(phenyl)methanol m34

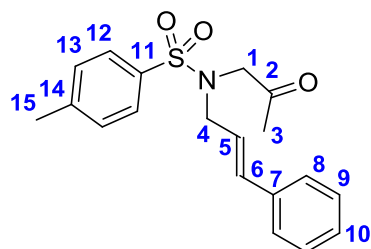
$R_f = 0.25$ (pentane/ Et_2O , 1:1).

IR (neat): $\nu = 3512$ (ν_{OH}), 2927, 2857 ($\nu_{\text{C-H alkyl}}$), 1668 ($\nu_{\text{C=C gem-disubstituted}}$), 1600, 1496 ($\nu_{\text{C=C aryl}}$), 1475 ($\delta_{\text{C-H CH}_3}$), 1456 ($\nu_{\text{C=C aryl}}$), 1344 ($\nu_{\text{S=O sulfone}}$), 1309 ($\nu_{\text{C-O}}$), 1162 ($\nu_{\text{S=O sulfone}}$), 1097 (δ_{OH}).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.69 (d, $J = ?$ Hz, 2H, H-12), 7.39-7.18 (m, 7H, H-13 + H-8 + H-9 + H-10), 4.92 (m, 1H, H-5), 4.66

(dd, $J = 6.6, 2.9$ Hz, 1H, H-6), 4.55 (m, 1H, H-5), 3.80 (tt, $J = 2.2, 1.1$ Hz, 2H, H-4), 3.53 (dd, $J = 9.9, 5.3$ Hz, 1H, H-1), 3.23 (dd, $J = 9.9, 7.3$ Hz, 1H, H-1), 3.03-2.87 (m, 1H, H-3), 2.43 (s, 3H, H-15), 2.21-2.05 (m, 1H, OH).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 144.3 (C-2), 143.8 (C-14), 141.9 (C-7), 132.7 (C-11), 129.8 (C-13), 128.5 (C-9 + C-10), 128.0 (C-12), 126.4 (C-8), 109.5 (C-5), 74.0 (C-6), 52.8 (C-1), 50.6 (C-3), 49.6 (C-4), 21.7 (C-15).



Chemical Formula: $\text{C}_{19}\text{H}_{21}\text{NO}_3\text{S}$
 Molecular Weight: 343,4 $\text{g}\cdot\text{mol}^{-1}$

N-cinnamyl-4-methyl-N-(2-oxopropyl)benzenesulfonamide m32

$R_f = 0.30$ (pentane/ Et_2O , 1:1).

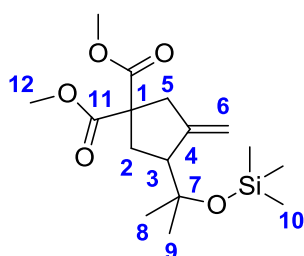
IR (neat): $\tilde{\nu} = 2924, 2854$ ($\nu_{\text{C-H alkyl}}$), 1735 ($\nu_{\text{C=O}}$), 1645 ($\nu_{\text{C=C}}$), 1600, 1457 ($\nu_{\text{C=C Ar}}$), 1338 ($\nu_{\text{S=O sulfone}}$), 1300 ($\delta_{\text{C-H vinyl}}$), 1158 ($\nu_{\text{S=O sulfone}}$), 955 ($\delta_{\text{C-H vinyl}}$), 815, 742, 700 ($\delta_{\text{C-H Ar}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.69 (d, $J = ?$ Hz, H-**12**), 7.34-7.12 (m, 7H, H_{Ar}), 6.36 (dt, $J = 15.9, 1.3$ Hz, 1H, H-**6**), 5.94 (dt, $J = 15.8, 7.1$ Hz, 1H, H-**5**), 4.00-3.83 (m, 4H, H-**1** + H-**4**), 2.38 (s, 3H, H-**15**), 2.10 (s, 3H, H-**3**).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 204.0 (C-**2**), 143.8 (C-**14**), 136.4 (C-**11**), 135.9 (C-**7**), 135.2 (C-**6**), 129.8 (C-**13**), 128.8 (C-**9**), 128.3 (C-**10**), 127.6 (C-**12**), 126.6 (C-**8**), 123.2 (C-**5**), 55.8 (C-**1** or C-**4**), 51.1 (C-**1** or C-**4**), 27.2 (C-**3**), 21.7 (C-**15**).

HRMS (ES+) calcd for $[(\text{C}_{19}\text{H}_{21}\text{NO}_3\text{S} + \text{Na})^+]$:366.1134; found:366.1141.

Dimethyl 3-methylene-4-(2-((trimethylsilyl)oxy)propan-2-yl)cyclopentane-1,1-dicarboxylate **m46**



$\text{C}_{16}\text{H}_{28}\text{O}_5\text{Si}$
328,5 g.mol $^{-1}$
Yellow oil
36%

The substrate **m15** (41 mg, 0.160 mmol, 1 equiv.) was dissolved in dichloromethane (0.5 mL). At room temperature, HMDS (35 μL , 0.160 mmol, 1 equiv.) and one drop of TMSCl were successively added. Then, the reaction mixture was heated to 40°C and let stirring at this temperature overnight. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 7:3), after what the reaction mixture was diluted with Et_2O , and the resulting organic solution washed with brine (3x), dried over MgSO_4 , filtered through a glass frit and concentrated under vacuum to afford a yellow oil as the crude product. The latter was purified by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9.5:0.5) to yield the pure product as a yellow oil (19 mg, 0.0578 mmol, 36%).

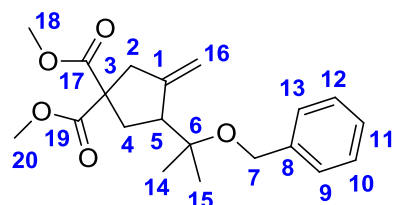
$R_f = 0.29$ (*n*-Pent/EtOAc, 9.5:0.5).

IR (neat): $\tilde{\nu} = 2954, 2844$ ($\nu_{\text{C-H alkyl}}$), 1737 ($\nu_{\text{C=O}}$), 1658 ($\nu_{\text{C=C}}$), 1462, 1434, 1382 ($\delta_{\text{C-H alkyl}}$), 1365, 1332, 1302, 1273 ($\nu_{\text{C-O}}$), 892 ($\delta_{\text{C-H vinyl}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 5.05-5.00 (m, 1H, H-**6**), 4.98-4.92 (m, 1H, H-**6**), 3.73 (s, 3H, H-**12**), 3.71 (s, 3H, H-**12**), 2.88 (dq, $J = 14.8, 2.7$ Hz, 1H, H-**5**), 2.78 (d $J = 14.9$ Hz, 1H, H-**5**), 2.58 (qd, $J = 8.6, 1.4$ Hz, 2H, H-**2**).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 172.3, 172.2 (C-**11**), 148.9 (C-**4**), 110.8 (C-**6**), 75.8 (C-**1** or C-**4**), 58.9 (C-**1** or C-**4**), 53.6 (C-**3**), 52.8 (C-**12**), 43.7 (C-**5**), 36.1 (C-**2**), 28.3 (C-**8** or C-**9**), 27.3 (C-**8** or C-**9**), 2.6 (C-**10**).

HRMS (ESI) calcd for $[(C_{16}H_{28}O_5Si + Na)^+]$:351.1598; found:351.1604.



$C_{20}H_{26}O_5$
346,4 g.mol⁻¹
Yellow oil
27%

Dimethyl 3-(2-(benzyloxy)propan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate m54

The catalyst IPrAuCl (5 mg, 0.0084 mmol, 2 mol%) was introduced, followed by the addition of AgSbF₆ (0.0084 mmol, 2 mol%) as a solution in dichloromethane (0.75 ml, C = 4 mg/mL). Then MeOH (0.17 mL, 4.2 mmol, 10 equiv.) and benzyl alcohol (0.43 mL, 4.2 mmol, 10 equiv.) were added. Finally, the substrate **m15** (100 mg, 0.420 mmol, 1 equiv.) was introduced as a solution in dichloromethane (3 x 1 mL).

The volume of dichloromethane was completed to 5 mL (C = 0.084 M), and the reaction was let stirring at room temperature overnight, in dark. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 8:2). Then, the reaction mixture was filtered through a short pad of silica and concentrated under vacuum to afford a yellowish liquid as the crude product. The latter was purified by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9.5:0.5) to yield the pure product as a yellow oil (39 mg, 0.113 mmol, 27%).

$R_f = 0.39$ (*n*-Pent/EtOAc, 8:2). $R_f = 0.14$ (*n*-Pent/EtOAc, 9.5:0.5).

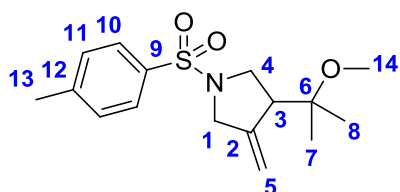
IR (neat): $\tilde{\nu} = 2975, 2953, 2848$ ($\nu_{C-H \text{ alkyl}}$), 1732 ($\nu_{C=O}$), 1657 ($\nu_{C=C}$), $1606, 1497, 1453$ ($\nu_{C=C \text{ Ar}}$), $1471, 1433, 1385, 1365$ ($\delta_{C-H \text{ alkyl}}$), $1332, 1300, 1272, 1203$ (ν_{C-O}).

¹H NMR (CDCl₃, 300 MHz): δ 7.38-7.16 (m, 5H, H_{Ar} from H-**9** to H-**13**), 5.10-5.00 (m, 2H, H-**16**), 4.46 (s, 2H, H-**7**), 3.73 (s, 3H, H-**18** or H-**20**), 3.72 (s, 3H, H-**18** or H-**20**), 3.03-2.80 (m, 3H, H-**4**+H-**5**), 2.63 (ddd, $J = 13.4, 8.5, 1.9$ Hz, AH, H-**2**), 2.12 (dd, $J = 13.5, 9.3$ Hz, 1H, H-**2**), 1.30 (s, 3H, H-**14** or H-**15**), 1.24 (s, 3H, H-**14** or H-**15**).

¹³C NMR (CDCl₃, 75 MHz): δ 172.2 (C-**17** or C-**19**), 172.1 (C-**17** or C-**19**), 148.3 (C-**1**), 139.7 (C-**8**), 128.4, 127.3, 127.2 (C_{Ar} from C-**9** to C-**13**), 110.9 (C-**16**), 77.5 (C-**6**), 63.6 (C-**7**), 58.8 (C-**3**), 50.2 (C-**5**), 43.6 (C-**2**), 36.2 (C-**4**), 23.4 (C-**14** or C-**15**), 22.8 (C-**14** or C-**15**).

HRMS (ESI) calcd for $[(C_{20}H_{26}O_5 + Na)^+]$:369.1672; found:369.1660.

3-(2-methoxypropan-2-yl)-4-methylene-1-tosylpyrrolidine m29



$C_{16}H_{23}NO_3S$
 309,4 g.mol⁻¹
 White solid
 81%

t-Bu₂P(OH)AuCl **m4** (3 mg, 0.00722 mmol, 2 mol%) and AgSbF₆ (3 mg, 0.00722 mmol, 2 mol%) were introduced, then dissolved into methanol (0.72 mL). Instantly, a dark solution was obtained. After a 5 minute-stirring, the substrate **m12** (100 mg, 0.361 mmol, 1.0 equiv.) was introduced, followed by distilled water (0.10 mL). The solution was let stirring at room temperature under argon

and protected from light. Completion of the reaction was monitored by TLC (Pent/Et₂O, 7.5:2.5). After 20 hours, the reaction mixture was filtered over a pad of silica. The flask and silica were rinsed with a large amount of Et₂O. Then the filtrate was concentrated under vacuum to give a brown oil as the crude product. The latter was further purified by flash chromatography (Pent/Et₂O, 6:4). The pure product (91 mg, 0.294 mmol, 81%) was obtained as a white solid.

R_f = 0.28 (Pentane/Et₂O, 6:4).

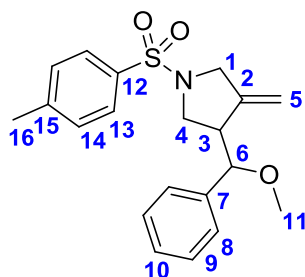
Mp: 66°C.

IR (neat): ν = 2936 (ν_{OH}), 1664 ($\nu_{C=C}$ gem-disubstituted), 1600, 1463 ($\nu_{C=C}$ Ar), 1384 (δ_{C-H} CH₃), 1344, 1160 ($\nu_{S=O}$ sulfone).

¹H NMR (CDCl₃, 300 MHz) δ 7.71 (d, J = 8.2 Hz, 2H-**10**), 7.36 – 7.28 (m, 2H, H-**11**), 5.04 (q, J = 2.1 Hz, 2H, H-**5**), 3.78 (dt, J = 3.2, 1.5 Hz, 2H, H-**1**), 3.46 – 3.22 (m, 2H, H-**4**), 3.09 (s, 3H, H-**14**), 2.85 – 2.74 (m, 1H, H-**3**), 2.42 (s, 3H, H-**13**), 1.12 (s, 3H, H-**7** or H-**8**), 1.00 (s, 3H, H-**7** or H-**8**).

¹³C NMR (CDCl₃, 101 MHz) δ 144.8 (C-**9**), 143.7 (C-**12**), 133.0 (C-**2**), 129.7 (C-**11**), 128.0 (C-**10**), 110.8 (C-**5**), 76.3 (C-**6**), 53.5 (C-**1**), 51.0 (C-**3**), 49.8 (C-**4**), 49.2 (C-**14**), 22.4 (C-**7** or C-**8**), 21.9 (C-**7** or C-**8**), 21.7 (C-**13**).

3-(methoxy(phenyl)methyl)-4-methylene-1-tosylpyrrolidine **m31**



$C_{20}H_{23}NO_3S$
 357,5 g.mol⁻¹
 35%

R_f = 0.29 (Pentane/Et₂O, 7.5:2.5).

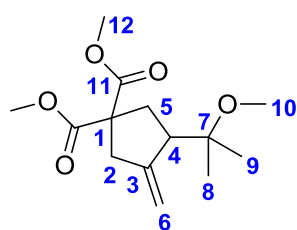
IR (neat): ν = 2933, 2857 (ν_{C-H} alkyl), 1666 ($\nu_{C=C}$ gem-disubstituted), 1598, 1494, 1454 ($\nu_{C=C}$ Ar), 1399 (δ_{C-H} vinyl), 1345 ($\nu_{S=O}$ sulfone), 1306, 1290 (ν_{C-O}), 1160 ($\nu_{S=O}$ sulfone), 904 (δ_{C-H} vinyl), 842, 763, 703 (δ_{C-H} Ar).

¹H NMR (CDCl₃, 300 MHz) δ 7.73 (d, J = 8.3 Hz, 2H, H-**13**), 7.40-7.22 (m, 5H, H-**14** + H-**9** + H-**10**), 7.21-7.10 (m, 2H, H-**8**), 4.76 (d, J = 2.0 Hz, 1H, H-**5**), 4.20 (d, J = 2.0 Hz, 1H, H-**5**), 3.91 (d, J = 8.2 Hz, 1H, H-**6**),

3.88-3.80 (m, 1H, H-1), 3.75-3.63 (m, 2H, H-1 + H-4), 3.29-3.18 (m, 1H, H-4), 3.10 (s, 3H, H-11), 2.43 (s, 3H, H-16).

¹³C NMR (CDCl₃, 100 MHz) δ 143.7 (C-15), 143.6 (C-2), 139.5 (C-7), 133.0 (C-12), 129.8 (C-14), 128.3 (C-9), 128.1 (C-10), 128.0 (C-13), 127.7 (C-8), 110.1 (C-5), 83.9 (C-6), 57.0 (C-11), 52.4 (C-1), 50.6 (C-3), 50.6 (C-4), 21.7 (C-16).

Dimethyl 3-(2-methoxypropan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate m28



C₁₄H₂₂O₅
270,3 g.mol⁻¹
Yellow oil
89%

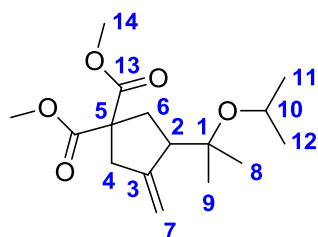
Purification by flash chromatography (Pent/Et₂O, 8:2) afforded the pure product (101 mg; 0.374 mmol; 89%) as a yellow oil. R_f = 0.25 (Pentane/Et₂O, 8:2).

IR (neat): ν = 2953 (ν_{C-H alkyl}), 1732 (ν_{C=O esters}), 1656 (ν_{C=C gem-disubstituted}), 1434, 1381 (δ_{C-H CH₃}).

¹H NMR (CDCl₃, 400 MHz) δ 5.08 – 5.01 (m, 1H, H-6), 5.00 – 4.94 (m, 1H, H-6), 3.72 (s, 3H, H-12), 3.71 (s, 3H, H-12), 3.18 (s, 3H, H-10), 2.95 – 2.79 (m, 3H, H-2+H-4), 2.55 (ddd, J = 13.5, 8.5, 1.8 Hz, 1H, H-5), 2.01 (dd, J = 13.5, 9.3 Hz, 1H, H-5), 1.18 (s, 3H, H-8 or H-9), 1.12 (s, 3H, H-8 or H-9).

¹³C NMR (CDCl₃, 101 MHz) δ 172.2, 172.1 (C-11), 148.4 (C-3), 110.7 (C-6), 76.9 (C-7), 58.7 (C-1), 52.9, 52.8 (C-12), 49.3 (C-4), 49.2 (C-10), 43.5 (C-2), 36.2 (C-5), 22.8 (C-8 or C-9), 22.3 (C-8 or C-9).

Dimethyl 3-(2-isopropoxypropan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate m53



C₁₆H₂₆O₅
298,4 g.mol⁻¹
Pale yellow oil
10%

IR (neat): ν = 2973 (ν_{C-H alkyl}), 1737 (ν_{C=O esters}), 1657 (ν_{C=C}), 1435, 1382, 1367 (δ_{C-H alkyl}), 895 (δ_{C-H vinyl}).

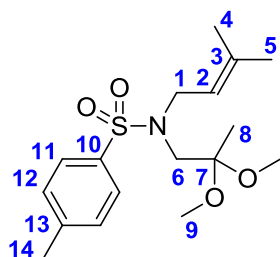
¹H NMR (CDCl₃, 300 MHz) δ 5.09-5.04 (m, 1H, H₇), 5.04-4.98 (m, 1H, H-7), 3.81 (hept, J = 6.1 Hz, 1H, H-10), 3.72 (s, 3H, H-14), 3.71 (s, 3H, H-14), 2.98-2.86 (m, 1H, H-4), 2.86-2.76 (m, 1H, H-4), 2.70 (tq, J = 8.8, 2.0 Hz, 1H, H-2), 2.56 (ddd, J = 13.2, 8.4, 1.8 Hz, 1H, H-6), 2.03

(dd, $J = 13.2, 9.0$ Hz, 1H, H-6), 1.16 (s, 3H, H-8 or H-9), 1.13 (s, 3H, H-8 or H-9), 1.09 (d, $J = 6.1$ Hz, 6H, H-11+H-12).

^{13}C NMR (75 MHz, CDCl_3) δ 172.3, 172.3 (C-13), 148.6 (C-3), 110.8 (C-7), 63.4 (C-10), 58.7 (C-5), 52.8 (C-1), 51.8 (C-10), 43.5 (C-4), 36.3 (C-6), 25.2 (C-11 or C-12), 25.0 (C-11 or C-12), 24.2 (C-8 or C-9), 22.8 (C-8 or C-9).

HRMS (ESI) calcd for $[(\text{C}_{16}\text{H}_{26}\text{O}_5 + \text{Na})^+]$:321.1672; found:321.1685.

***N*-(2,2-dimethoxypropyl)-4-methyl-*N*-(3-methylbut-2-en-1-yl)benzenesulfonamide m30**



$\text{C}_{17}\text{H}_{27}\text{NO}_4\text{S}$
341,5 $\text{g}\cdot\text{mol}^{-1}$
Yellow oil
12%

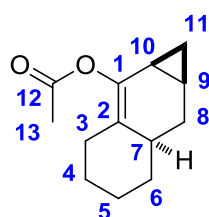
IR (neat): $\nu = 2927, 2833$ ($\nu_{\text{C-H alkyl}}$), 1668 ($\nu_{\text{C=C}}$), 1599, 1494, 1450 ($\nu_{\text{C=C Ar}}$), 1384 ($\delta_{\text{C-H alkyl}}$), 1340, 1157 ($\nu_{\text{S=O sulfone}}$), 1107, 1091, 1076, 1046 ($\nu_{\text{C-N alkyl amine}}$), 836 ($\delta_{\text{C-H Ar}}$), 815, 802 ($\delta_{\text{C-H vinyl}}$).

^1H NMR (CDCl_3 , 400 MHz) δ 7.67 (d, $J = 8.3$ Hz, 2H, H-11), 7.27 (d, $J = 8.0$ Hz, 2H, H-12), 4.76 (tt, $J = 6.7, 1.3$ Hz, 1H, H-2), 3.97 (d, $J = 6.7$ Hz, 2H, H-1), 3.29 (s, 2H, H-6), 3.18 (s, 6H, H-9), 2.4 (s, 3H, H-14), 1.59 (s, 3H, H-4+H-5), 1.57 (s, 3H, H-4+H-5), 1.40 (s, 3H, H-8).

^{13}C NMR (CDCl_3 , 101 MHz) δ 143.1 (C-13), 138.2 (C-10), 136.3 (C-3), 129.6 (C-12), 127.5 (C-11), 119.0 (C-2), 102.1 (C-7), 50.2 (C-6), 48.5 (C-9), 46.2 (C-1), 25.9 (C-4 or C-5), 21.6 (C-14), 20.2 (C-8), 17.9 (C-4 or C-5).

HRMS (ES+) calcd for $[(\text{C}_{17}\text{H}_{27}\text{NO}_4\text{S} + \text{Na})^+]$:364.1553; found:364.1554.

1a,3,4,5,6,6a,7,7a-octahydro-1H-cyclopropa[b]naphthalen-2-yl acetate m49



$\text{C}_{13}\text{H}_{18}\text{O}_2$
206,3 $\text{g}\cdot\text{mol}^{-1}$
Yellow oil

262 42%

The catalyst IPrAuCl (16 mg, 0.0243 mmol, 5 mol%) was introduced. Then, AgSbF_6 (9 mg, 0.0243 mmol, 5 mol%) was added as a solution in dichloromethane (1.3 mL, $C = 6.8$ mg/mL). Finally, the substrate **m48** (100 mg, 0.485 mmol, 1 equiv.) was introduced as a solution in dichloromethane (4 x 1 mL) and the volume of dichloromethane was completed to 19.4 (C =

0.025 M). An orange solution was obtained, that was heated to reflux and stirred in the dark at room temperature overnight. After the completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 9:1), the reaction mixture was filtered through a short pad of silica and concentrated under vacuum to yield the crude product as an orange oil. The latter was then purified by flash column chromatography on silica gel to afford the pure product as a yellow oil (42 mg, 0.204 mmol, 42%).

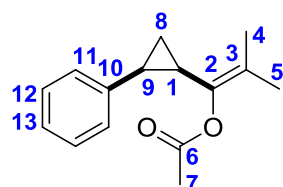
$R_f = 0.18$ (*n*-Pent/EtOAc, 9.8:0.2).

IR (neat): $\tilde{\nu} = 2922, 2851$ ($\nu_{\text{C-H alkyl}}$), 1753 ($\nu_{\text{C=O}}$), 1676 ($\nu_{\text{C=C}}$), 1604, 1498, 1459 ($\nu_{\text{C=C Ar}}$)

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 2.53-2.39 (m, 1H, H-5), 2.32-2.10 (m, 5H, H-3 + H-7 + H-13), 1.77-1.61 (m, 3H, H-4 + H-6 + H-8), 1.60-1.45 (m, 1H, H-5), 1.39 (ddd, $J = 14.3, 4.4, 2.7$ Hz, 1H, H-3), 1.34-1.10 (m, 4H, H-1 + H-4 + H-6 + H-9), 1.10-0.94 (m, 1H, H-8), 0.88 (td, $J = 8.3, 4.1$ Hz, 1H, H-11), 0.40 (dt, $J = 5.8, 4.2$ Hz, 1H, H-11).

$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 169.6 (C-12), 141.7 (C-1), 124.2 (C-2), 38.3 (C-8), 36.1 (C-7), 28.2 (C-3), 27.2 (C-4 or C-6), 26.9 (C-5), 26.6 (C-4 or C-6), 21.0 (C-13), 18.6 (C-11), 12.5 (C-9 or C-10), 12.2 (C-9 or C-10).

2-methyl-1-((1R,2S)-2-phenylcyclopropyl)prop-1-en-1-yl acetate **m23**



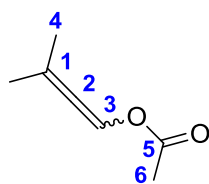
$\text{C}_{15}\text{H}_{18}\text{O}_2$
230,3 $\text{g}\cdot\text{mol}^{-1}$
Yellow oil
31%

IR (neat): $\tilde{\nu} = 2924$ ($\nu_{\text{C-H alkyl}}$), 1753 ($\nu_{\text{C=O}}$), 1676 ($\nu_{\text{C=C}}$), 1604, 1498, 1459 ($\nu_{\text{C=C Ar}}$), 1370 ($\delta_{\text{C-H alkyl}}$), 734, 700 ($\delta_{\text{C-H Ar}}$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.25-7.18 (m, 2H, H-12), 7.18-7.10 (m, 2H, H-13), 7.08-7.01 (m, 2H, H-11), 2.36-2.20 (m, 2H, H-1 + H-9), 2.04 (s, 3H, H-7), 1.48 (d, $J = 0.6$ Hz, 3H, H-4 or H-5), 1.42 (d, $J = 1.4$ Hz, 3H, H-4 or H-5), 1.30-1.21 (m, 1H, H-8), 1.03 (td, $J = 6.4, 5.3$ Hz, 1H, H-8).

$^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ 169.5 (C-6), 139.4 (C-10), 138.4 (C-2), 127.7 (C-12), 127.5 (C-11), 125.7 (C-13), 123.4 (C-3), 24.3, 21.8 (C-1 + C-9), 20.7 (C-7), 18.7, 17.6 (C-4 + C-5), 11.6 (C-8).

3-methylbuta-1,2-dien-1-yl acetate **m26**



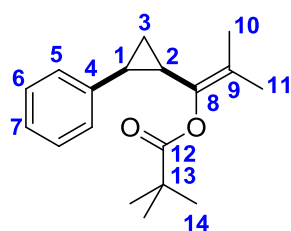
$C_7H_{10}O_2$
126,2 g.mol⁻¹
Yellow oil

IR (neat): $\nu = 2957, 2925, 2855$ ($\nu_{C-H \text{ alkyl}}$), 1732 ($\nu_{C=O}$), $1461, 1373$ ($\delta_{C-H \text{ alkyl}}$), 1263 (ν_{C-O}).

¹H NMR ($CDCl_3$, 400 MHz) δ 7.21 (hept, $J = 1.9$ Hz, 1H, H-3), 2.12 (s, 3H, H-6), 1.83 (d, $J = 2.0$ Hz, 6H, H-4).

¹³C NMR ($CDCl_3$, 101 MHz) δ 190.0 (C-2), 170.0 (C-5), 111.8 (C-1), 108.3 (C-3), 22.0 (C-4), 21.1 (C-6).

cis-2-methyl-1-(2-phenylcyclopropyl)prop-1-en-1-yl pivalate m25



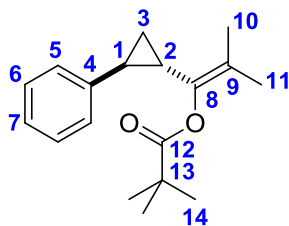
$C_{18}H_{24}O_2$
272,4 g.mol⁻¹
Yellow oil 64%

IR (neat): $\nu = 2930, 2871$ ($\nu_{C-H \text{ alkyl}}$), 1740 ($\nu_{C=O}$), 1695 ($\nu_{C=C}$), $1605, 1497$ ($\nu_{C=C \text{ Ar}}$), 1479 ($\delta_{C-H \text{ alkyl}}$), 1460 ($\nu_{C=C \text{ Ar}}$), 1366 ($\delta_{C-H \text{ alkyl}}$), $736, 699$ ($\delta_{C-H \text{ Ar}}$).

¹H NMR ($CDCl_3$, 400 MHz) δ 7.25-7.18 (m, 2H, H-6), 7.17-7.10 (m, 1H, H-7), 7.06-7.00 (m, 2H, H-5), 2.33-2.21 (m, 2H, H-1+H-2), 1.48 (s, 3H, H-10), 1.41 (s, 3H, H-11), 1.31-1.17 (m, 1H, H-3), 1.22 (s, 9H, H-14), 1.00 (td, $J = 6.4, 5.3$ Hz, 1H, H-3).

¹³C NMR ($CDCl_3$, 101 MHz) δ 176.9 (C-12), 139.6 (C-4), 138.2 (C-8), 127.6 (C-6), 127.4 (C-5), 125.6 (C-7), 123.2 (C-9), 39.0 (C-13), 27.4 (C-14), 24.1 (C-1), 21.9 (C-2), 18.7 (C-10), 17.4 (C-11), 11.9 (C-3).

trans-2-methyl-1-(2-phenylcyclopropyl)prop-1-en-1-yl pivalate m25



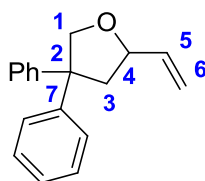
C₁₈H₂₄O₂
272,4 g.mol⁻¹
Yellow oil
4%

IR (neat): ν = 2962, 2928, 2859 ($\nu_{\text{C-H alkyl}}$), 1743 ($\nu_{\text{C=O}}$), 1692 ($\nu_{\text{C=C}}$), 1605, 1499 ($\nu_{\text{C=C Ar}}$), 1479 ($\delta_{\text{C-H alkyl}}$), 1460 ($\nu_{\text{C=C Ar}}$), 1396 ($\nu_{\text{C-O}}$), 1367 ($\delta_{\text{C-H alkyl}}$), 755, 697 ($\delta_{\text{C-H Ar}}$).

¹H NMR (CDCl₃, 400 MHz) δ 7.29-7.22 (m, 2H, H-6), 7.19-7.12 (m, 1H, H-7), 7.11-7.05 (m, 2H, H-5), 2.08-1.94 (m, 2H, H-1+H-2), 1.79 (s, 3H, H-10), 1.55 (s, 3H, H-11), 1.29 (s, 9H, H-14), 1.11 (t, J = 7.4 Hz, 2H, H-3).

¹³C NMR (CDCl₃, 101 MHz) δ 176.7 (C-12), 142.2 (C-4), 140.8 (C-8), 128.5 (C-9), 126.0 (C-6), 125.9 (C-5), 120.5 (C-7), 39.2 (C-13), 27.5 (C-14), 23.5 (C-1 or C-2), 23.4 (C-1 or C-2), 18.9 (C-10), 18.0 (C-11), 14.7 (C-3).

4,4-diphenyl-2-vinyltetrahydrofuran m56



C₁₈H₁₈O
250,3 g.mol⁻¹
Yellow oil
87%

The catalyst IPrAuCl (5 mg, 0.008 mmol, 2 mol%) and AgSbF₆ (3 mg, 0.008 mmol, 2 mol%) were introduced and dissolved in dichloromethane (16 mL, C = 0.025 M). Then, EtOH (0.12 ml, 2 mmol, 5 equiv.) and the substrate (100 mg, 0.4 mmol, 1 equiv.) were successively added and the reaction mixture was stirred in the dark at room temperature overnight. After the completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 8.5:1.5), the reaction mixture was filtered through a short pad of silica rinsed with EtOAc and concentrated under vacuum to give a thick yellow oil as the crude product. After purification by flash column chromatography on silica gel (*n*-Pent/EtOAc, 9.8:0.2 -> 8.5:1.5 -> 0:10), the pure product was obtained as a yellow oil (87 mg, 0.348 mmol, 87%).

R_f = 0.30 (*n*-Pent/EtOAc, 8.5:1.5).

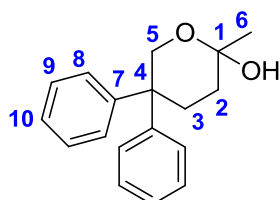
IR (neat): $\tilde{\nu}$ = 2927, 2865 ($\nu_{\text{C-H alkyl}}$), 1644 ($\nu_{\text{C=C}}$), 1599, 1585, 1494, 1446 ($\nu_{\text{C=C Ar}}$), 1425 ($\delta_{\text{C-H vinyl}}$), 1336, 1257 ($\nu_{\text{C-O}}$), 889 ($\delta_{\text{C-H vinyl}}$), 757, 699 ($\delta_{\text{C-H Ar}}$).

¹H NMR (CDCl₃, 400 MHz) δ 7.38-7.11 (m, 10H, H_{Ar}), 5.90 (ddd, J = 17.1, 10.2, 6.9 Hz, 1H, H-5), 5.24 (dt, J = 17.1, 1.4 Hz, 1H, H-6), 5.11 (ddd, J = 10.3, 1.6, 1.0 Hz, 1H, H-6), 4.67 (dd, J = 8.7, 1.2 Hz, 1H, H-1), 4.44 (dddd, J = 9.2, 7.1, 6.1, 1.1 Hz, 1H, H-4), 4.16 (d, J = 8.7 Hz, 1H, H-1), 2.66 (ddd, J = 12.2, 6.0, 1.2 Hz, 1H, H-3), 2.45 (dd, J = 12.2, 9.7 Hz, 1H, H-3).

¹³C NMR (CDCl₃, 100 MHz) δ 146.1, 145.7 (C-7), 139.0 (C-5), 128.6, 128.5, 127.3, 126.7, 126.5 (CH_{Ar}), 116.0 (C-6), 79.9 (C-4), 77.2 (C-1), 56.3 (C-2), 45.3 (C-3).

HRMS (ES+) calcd for $[(C_{16}H_{28}O_5Si + Na)^+]$:351.1598; found:351.1604.

2-methyl-5,5-diphenyltetrahydro-2H-pyran-2-ol m59



$C_{18}H_{20}O_2$
268,4 g.mol⁻¹

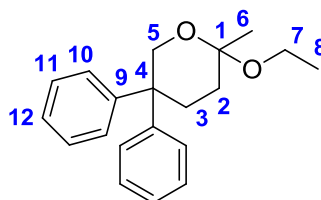
IR (neat): $\tilde{\nu}$ = 3400 (ν_{OH}), 2931, 2875, 2852 ($\nu_{C-H \text{ alkyl}}$), 1599, 1581, 1494, 1446 ($\nu_{C=CAr}$), 1378 (ν_{C-O}), 1152 (δ_{OH}), 755, 699 ($\delta_{C-H Ar}$).

1H NMR ($CDCl_3$, 300 MHz) δ 7.47-7.37 (m, 2H, CH_{Ar}), 7.37-7.11 (m, 8H, CH_{Ar}), 4.29 (dd, J = 12.0, 2.9 Hz, 1H, H-5), 4.06 (d, J = 12.0 Hz, 1H, H-5), 2.83 (td, J = 13.2, 3.7 Hz, 1H, H-3), 2.25 (dq, J = 12.9 Hz, 3.6 Hz, 1H, H-3), 2.04 (m, 1H, OH), 1.73 (dt, J = 13.6, 3.6 Hz, 1H, H-2), 1.49-1.35 (m, 1H, H-2), 1.39 (s, 3H, H-6).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.6, 145.4 (C-7), 128.6, 128.4, 128.2, 127.3 (C-8 + C-9), 126.4, 125.9 (C-10), 95.1 (C-1), 68.2 (C-5), 45.7 (C-4), 31.3 (C-2), 30.1 (C-6), 29.9 (C-3).

HRMS (ES+) calcd for $[(C_{18}H_{20}O_2 + Na)^+]$:291.1356; found:291.1364.

2-ethoxy-2-methyl-5,5-diphenyltetrahydro-2H-pyran m57



$C_{20}H_{24}O_2$
296,4 g.mol⁻¹

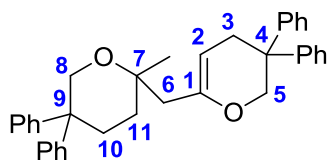
IR (neat): $\tilde{\nu}$ = 2971, 2930, 2875 ($\nu_{C-H \text{ alkyl}}$), 1598, 1581, 1494, 1445 ($\nu_{C=CAr}$), 1375 ($\delta_{C-H \text{ alkyl}}$), 753, 697 ($\delta_{C-H Ar}$).

1H NMR ($CDCl_3$, 300 MHz) δ 7.2-7.41 (m, 2H, CH_{Ar}), 7.39-7.14 (m, 8H, CH_{Ar}), 4.32 (dd, J = 11.9, 3.0 Hz, 1H, H-5), 3.78 (d, J = 11.9 Hz, 1H, H-5), 3.55 (q, J = 7.1 Hz, 2H, H-7), 2.90 (td, J = 3.8 Hz, 1H, H-3), 2.22 (dq, J = 12.7 Hz, 3.3 Hz, 1H, H-3), 1.76 (dt, J = 13.6 Hz, 3.5 Hz, 1H, H-2), 1.43 (td, J = 13.5 Hz, 3.7 Hz, 1H, H-2), 1.31 (s, 3H, H-6), 1.23 (t, J = 7.1 Hz, 3H, H-8).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.8 (C-9), 145.6 (C-9), 128.7 (C-11 or C-10), 128.4 (C-11 or C-10), 128.1 (C-11 or C-10), 127.2 (C-11 or C-10), 126.4 (C-12), 125.8 (C-12), 97.2 (C-1), 68.2 (C-5), 55.6 (C-7), 45.6 (C-4), 32.4 (C-2), 29.7 (C-3), 24.3 (C-6), 15.7 (C-8).

HRMS (ES+) calcd for $[(C_{20}H_{24}O_2 + Na)^+]$:319.1669; found:319.1660.

6-((2-methyl-5,5-diphenyltetrahydro-2H-pyran-2-yl)methyl)-3,3-diphenyl-3,4-dihydro-2H-pyran m58



$C_{36}H_{36}O_2$
 500,7 g.mol⁻¹
 Pale yellow solid
 50%

The catalyst β -CyDAuCl (25 mg, 0.008 mmol, 2 mol%) and AgSbF₆ (3 mg, 0.008 mmol, 2 mol%) were introduced first, as solutions in dichloromethane (0.28 mL and 0.60 mL respectively). The substrate (100 mg, 0.4 mmol, 1 equiv.) was then added in dichloromethane (3 x 1 mL). Finally, the volume of dichloromethane was completed to 16 mL (C = 0.025 M), and the reaction mixture was let stirring in dark at room temperature overnight. The completion of the reaction was monitored by TLC (*n*-Pent/EtOAc, 8.5:1.5). Then, the reaction mixture was filtered through a short pad of silica rinsed with EtOAc, and concentrated under vacuum. The pure product (50 mg, 0.0999 mmol, 50%) was obtained as a pale yellow solid after flash column chromatography on silica gel (*n*-Pent/EtOAc, 9.8:0.2 -> 8.5:1.5 -> 0:10).

$R_f = 0.16$ (*n*-Pent/EtOAc, 8.5:1.5).

Mp = 140°C.

IR (neat): $\tilde{\nu} = 2932, 2864$ (ν_{C-H} alkyl), 1677 ($\nu_{C=C}$), 1599, 1582, 1494, 1446 ($\nu_{C=C}$ Ar), 1467, 1376 (δ_{C-H} alkyl), 1335 (ν_{C-O}), 831 (δ_{C-H} vinyl), 751, 697 (δ_{C-H} Ar).

¹H NMR (CDCl₃, 300 MHz) δ 7.41-7.14 (m, 20H, H_{Ar}), 4.75 (t, $J = 3.8$ Hz, 1H, H-2), 4.44 (bs, 2H, H-5), 4.08 (q, $J = 12.4$ Hz, 2H, H-8), 2.78 (bs, 2H, H-3), 2.37 (m, 3H, H-10+H-6), 2.18 (d, $J = 13.7$ Hz, 1H, H-6), 1.48-1.25 (m, 1H, H-11), 1.24-1.11 (m, 1H, H-11), 1.08 (s, 3H, H-12).

¹³C NMR (CDCl₃, 75 MHz) δ 151.4 (C-1), 146.7, 146.5, 145.8, 145.6 (C_{quat}Ar), 128.3, 128.2, 128.2, 127.9, 127.3, 127.3, 126.4, 126.0, 126.0 (CH_{Ar}), 98.5 (C-2), 73.3 (C-7), 72.6 (C-5), 68.8 (C-8), 45.9 (C-9), 43.9 (C-4), 43.6 (C-6), 33.9 (C-3), 30.6 (C-10), 30.3 (C-11), 23.8 (C-12).

HRMS (ESI) calcd for ([C₃₆H₃₆O₂ + Na]⁺):523.2608; found:523.2594.

Abstract

The study of small molecule natural products provides some knowledge about organic chemistry and has an impact on biomedical research. Transition metal-catalyzed reactions have been frequently used to affect key transformations. Especially, there has been a noticeable trend during the past decade towards the use of homogeneous gold-catalyzed transformations. This work aims at the valorization of the gold-catalyzed rearrangement of propargyl acetates in the total syntheses of (\pm)-Valeneomerin B and (\pm)-Neomeranol. These compounds are sesquiterpenoid natural products, the synthesis of which has been envisioned from the preparation of a common intermediate resulting from the gold-catalyzed rearrangement of a propargyl acetate precursor. At the same time, the behaviour of new secondary phosphine oxide- and CNHC-capped cyclodextrin-gold(I) complexes has been studied, to try and achieve better control on the course of gold-catalyzed transformations.

Keywords gold catalysis / propargyl acetate rearrangement / total synthesis / natural products / secondary phosphine oxides / NHC-capped cyclodextrins / cycloisomerization