Gold(I)-Catalyzed Synthesis of Polycyclic Frameworks Related to Terpenes:
Selective Divergent Synthesis of Fused Carbocycles

by

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À ma famille,

mes parents Carole Nadeau et Mario Barabé

et mon frère Tommy Barabé…

Abstract

Gold catalysis has become an important tool to achieve highly chemoselective π-acid activation. Exceptional reactivity and selectivity are often encountered under mild reaction conditions. These properties have made gold(I) complexes suitable catalysts for tremendous applications in the total synthesis of natural products. The first chapter will highlight a number of total syntheses using gold catalysis as a key step.

The second chapter will cover our application of the gold(I)-catalyzed 6-*endo-dig* carbocyclization for the synthesis of bridgehead-substituted scaffolds and its use toward the synthesis of PPAP natural products. This research has opened our eyes to the utility of biphenylphosphine ligands, particularly JohnPhos, in gold(I)-catalysis.

The reactivity and selectivity exhibited by gold(I) complexes is modulated by the nature of the ancillary ligand. Recent research rationalizes the impact of these ligands on the divergent reactivity observed between cationic and carbenoid intermediates. Our desire to favor the 6-*endo-dig* pathway has led us toward the discovery of another example of the diagonal reactivity that NHC carbene and biphenylphosphine ligands can bring to gold(I)-catalysis. Chapter three will explain the development of a selective gold-catalyzed synthesis of fused carbocycles

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Our selective divergent synthesis of fused carbocycles, combined with the Diels–Alder reaction, has brought new synthetic opportunities. Chapter four will describe our approach toward the synthesis of various polycyclic diterpene-related frameworks. Starting with a unique linear precursor, we have developed a new “one-pot” process for the synthesis of three different polycyclic compounds related to the terpenoid family. The facile modulation of the linear precursor and the use of different dienophiles during the Diels–Alder reaction could enable the synthesis of diverse polycyclic analogues based on three principal frameworks.

The gold(I)-catalyzed synthesis of fused carbocycles reached some limitations during our study. Regioselective control was found to be substantially more challenging, with terminal alkynes or alkynes bearing a sterically and electronically neutral methyl substituent. In chapter five, we will

discuss how the complementarity of silver(I) catalysis to gold(I) catalysis enabled the selective divergent synthesis of three different fused carbocycles from a unique precursor. Moreover, copper(I) catalysis has given access to the 6-*endo-dig* pathway on terminal alkynes without the formation of a vinylidene intermediate.

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Chapter 1

Gold(I)-Catalysis as a Highly Chemoselective Lewis π-Acid in Total Synthesis of Complex Natural Products

1.1 Introduction

Complexity and selectivity are two words that perfectly reflect the modern goals of synthetic chemistry. The synthesis of extremely complex architectural structures is now routine in academic laboratories, and organic chemists design novel and powerful catalytic tools to achieve mechanistically complex and selective transformations.[1] Recent methodological advancements in organocatalysis, photocatalysis, and metal-catalyzed transformations have enabled new reactivity and disconnections that allow shortened, robust, and efficient synthetic routes. The important impact of metal-catalyzed transformations on the formation of carbon–carbon bonds in the art of total synthesis can be demonstrated by the work of recent Nobel laureates: one for ruthenium-catalyzed olefin metathesis and the other for palladium-catalyzed cross-coupling reactions. While catalysis has focused primarily on the chemistry of these main transition metals, almost all metals are known to be active in a catalytic transformation. Gold is one of the last metals to undergo extensive investigation and emerged rapidly as one of the most powerful catalytic tools in organic chemistry.[2] The reason for the extended neglect of gold catalysis is difficult to understand, considering that since the beginning of civilization gold has accompanied mankind in a variety of day-to-day activities.[3] Gold's economic and social values hinge on its prestige and durability. Some of the oldest and most beautiful art pieces are made of gold. Due to its durability, rarity, divisibility, and fungibility, gold was an early form of currency for many civilizations. Moreover, recent monetary systems are still based on the gold standard, which tends to accentuate its stability and value in our mind.

After more than a decade of extensive investigation, homogeneous gold catalysis has allowed unprecedented access to highly chemoselective π-lewis acid reactivity.[2] Gold complexes, with their high oxidation potentials, are far less prone to redox chemistry. Thus, gold(I) processes are found to proceed with greater selectivity and under milder reaction conditions than other transition metal complexes.[3]

Additionally, gold(I) processes can be conducted at lower temperatures and in the presence of water and air. Superior catalytic activity exhibited by gold complexes in π-lewis acid reactivity and its potential to stabilize cationic intermediates can be rationalized by relativistic effects.[4] Other "abnormal" electronic properties, including the high electronegativity and electron affinity, the large ionization potentials, and other physical properties such as its color also can be explained by relativistic effects. Relativistic effects in chemistry can be attributed qualitatively to the high speed of the electrons as they move near a heavy nucleus. The consequent mass increase will lead to an energetic stabilization and radial contraction of the s and p orbitals. The contraction of these orbitals brings a better shielding of the nucleus, thus leading to an energetic destabilization and expansion of d and f orbitals. These two relativistic effects are significant only in some heavy metals but reach a maximum in the periodic table with the electronic configuration of gold. This electronic perturbation results in a much smaller band gaps (2.38 eV) than with other metals, allowing blue visible light to be absorbed and produce its golden color. The relativistic contraction of the 6s orbital provides an explanation for the superior π-acidity of gold complexes, while energetic destabilization and expansion of the 5d orbital allows the delocalization of electronic density into carbon-based orbitals of sufficiently low energy, particularly into an empty orbital of a carbocation. This provides a rationalization for the carbenoid behavior often observed with gold complexes, and this effect depends highly on the nature of the ligand on the gold complex. Another consequence of the relativistic effects on gold complexes resides in its preference to adopt a linear, bicoordinate geometry. This last effect has provided spectacular ligand impacts on the outcome of the catalyzed reactions but has significantly increased the difficulty for asymmetric induction during the development of enantioselective transformations.

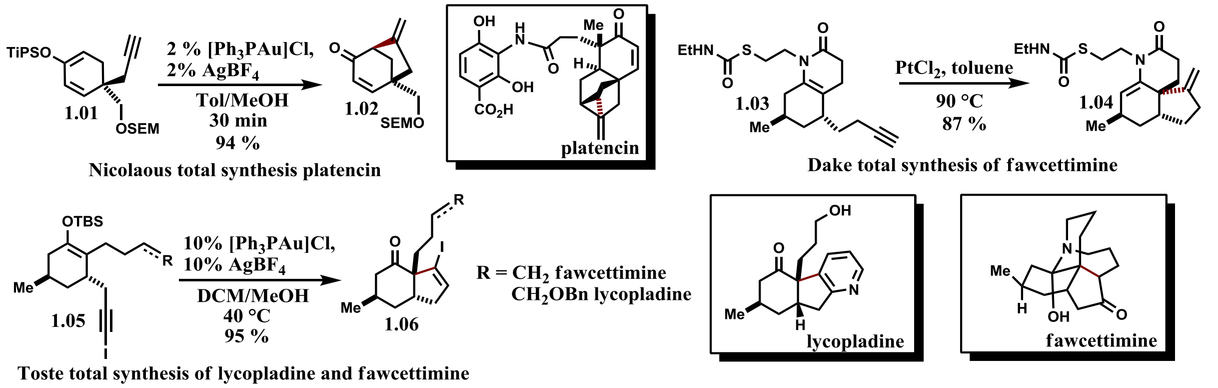
1.2 Gold(I)-catalysis in total synthesis of natural products

In the past decade, gold catalysis has been billed as one of the most important breakthroughs in organic synthesis.[2] Due to their selectivity, efficiency, robustness, and versatility, gold complexes are suitable catalysts for important applications in the total synthesis of natural products.[5] In fact, these highly chemoselective Lewis π-acid catalysts, which demonstrate reactivity under very mild conditions, tolerate the presence of various functional groups, minimizing protecting group manipulations.

Moreover, gold catalysts allow a rapid increase in molecular complexity and induce a high level of atom economy. Complex mechanistic cascades and chemoselective π-activation allow unique disconnections that often result in shorter and more efficient synthetic routes. The following section will highlight a number of total syntheses using homogeneous gold catalysis as the key step and will illustrate the wide utility of these catalysts. Syntheses that are closely related to the work described in this thesis will be presented first, followed by syntheses that undergo a mechanistically complex gold catalyzed cascade and finally syntheses where highly chemoselective π-activation is needed. A brief overview of essential concepts will reveal the synthetic potential of gold catalysis in the description of the presented examples.

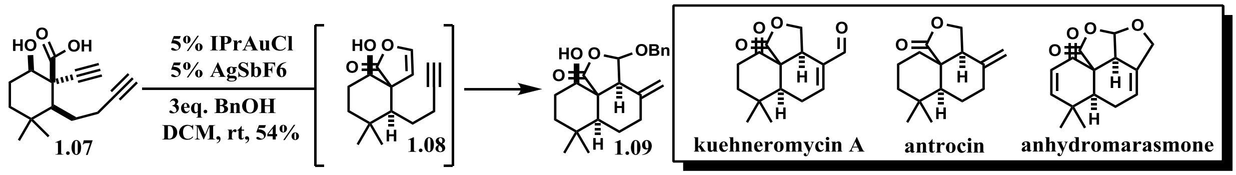
1.3 Gold-Catalyzed Conia-ene and related reactions

Gold catalysts act as soft Lewis acids and activate alkynes to allow nucleophilic additions. Cyclic enol ethers were found to be great nucleophilic partners and allow mild formation of carbon-carbon bonds. Toste and coworkers developed a gold catalyzed version of the Conia-ene reaction and extended the reaction scope to silyl enol ethers.[6] The utility of this new transformation was demonstrated by his group during the asymmetric synthesis of two Lycopodium alkaloids: lycopladine A and fawcettimine. Later, Nicolaou and coworkers used a gold(I)-catalyzed Conia-ene cyclization of a silyl enol ether (**1.01**) to construct [3.2.1]-bicyclic enone (**1.02**) in their route toward platencin.[7] On the other hand, enamines are not often used in gold catalysis, but Dake developed an equivalent strategy for the synthesis of fawcettimine. Cyclic enamine (**1.03**) was used as the nucleophilic partner and the transformation was catalyzed by a platinum complex.[8] Although this carbocyclization tolerates the formation of a quaternary center at the ring junction, only the synthesis of cyclopentene is reported, limiting the synthetic utility of these transformations.



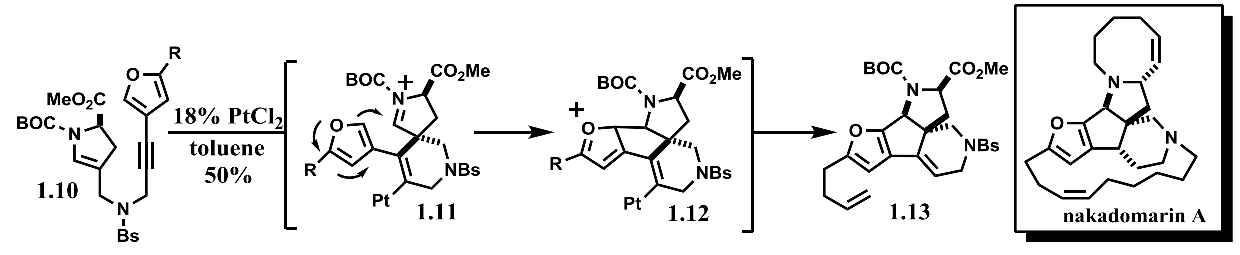
Scheme 1.01 *Total synthesis of platencin, lycopladine, and fawcettimine via 5-exo/endo-dig gold(I)-catalyzed carbocyclization (Conia-ene)*

Zhang and coworkers recently designed a cascade for the synthesis of three different drimane-type sesquiterpernes.[9] When diynes (**1.07**) were submitted to IPr gold(I) complex, a 5-*endo-dig* heterocyclization took place between the carboxylic acid and the first alkyne. This afforded cyclic enol ether (**1.08**), which is well set up to undergo a second cyclization. The 6-*exo-dig* carbocyclization allowed the formation of decalin compound (**1.09**), a common intermediate in the synthesis of the three natural products (**Scheme 1.02**). Interestingly, the presence of a strong σ-donor NHC ligand (**IPr**) on the gold complex was necessary to achieve the transformation with moderate yield.



Scheme 1.02 *Total synthesis of antrocin and related members via a 5-endo-dig gold(I)-catalyzed heterocyclization/6-exo-dig carbocyclization cascade by Zhang*

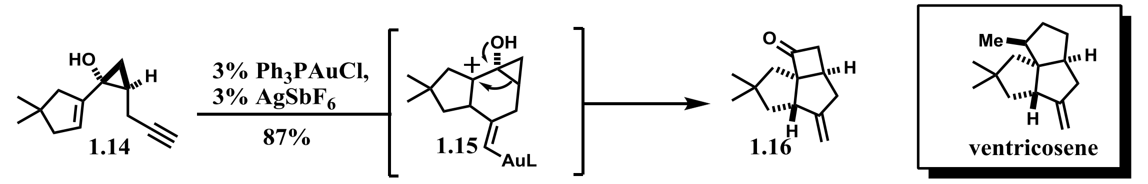
The last synthesis that inspired our work is based on the related platinum catalyzed process. A readily available enaminyne precursor (**1.10**) allows the stereoselective synthesis of the tetracyclic core (**1.13**) of the alkaloid nakadomain A.[10] An N-acyliminium ion (**1.11**), generated in situ upon addition of an enamide on an activated alkyne, triggers a Fridel-Crafts type cyclization leading to a formal [3+2] cycloaddition. The final two rings were formed by ring closing metathesis (RCM), using Grubb's first and second generation catalysts.



Scheme 1.03 *Total synthesis of nakadomarin A via a platinum catalyzed formal [3+2] cycloaddition by Zhai*

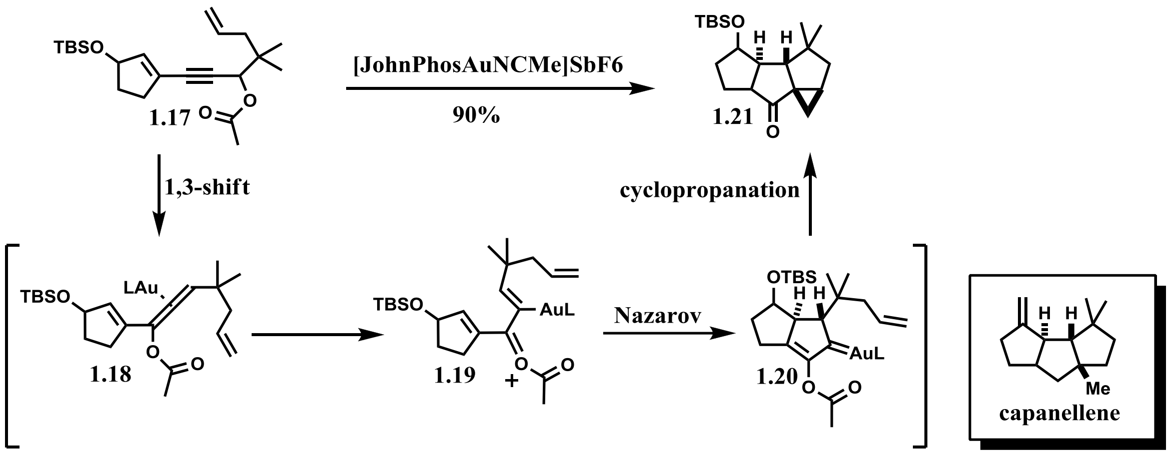
1.4 Gold-catalyzed mechanistically complex reaction cascade

The next syntheses will highlight mechanistically complex cascades initiated by gold catalysis. Upon π–activation of an alkyne, highly reactive cationic intermediates are generated. These can be designed to undergo further known cationic processes and lead to polycyclic structures relevant to the synthesis of natural products. Toste reported an early example of this concept for the synthesis of ventricosene.[11] After the initial 6-*exo-dig* cyclization of enyne (**1.14**), the tertiary carbenium (**1.15**) undergoes a stereoselective semi-pinacolic rearrangement delivering cyclobutanone (**1.16**) in high yield. The final angular triquinane system was then addressed via a second ring expansion.



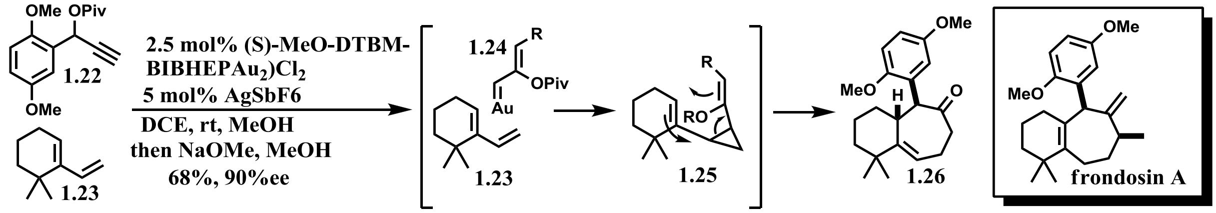
Scheme 1.04 *Total synthesis of ventricosene via a gold(I)-catalyzed 1,6 enyne cycloisomerizatiom/semi-pinacolic rearrangement cascade by Toste*

An illustration of mechanistically complex cationic cascades was reported by Malacria during the synthesis of capanelle.[12] A gold catalyzed rearrangement converts propargyl acetate (**1.17**) into acetoxy-allene (**1.18**), which is activated by the same catalyst to generate cationic intermediate (**1.19**). Electrocyclic Nazaroz cyclization of intermediate (**1.19**) delivers gold carbenoid intermediate (**1.20**), which undergoes a cyclopropanation with the tethered alkene. The resulting product (**1.21**) isolated in 90% yield was finally elaborated into the linear triquinane capanellene.



Scheme 1.05 *Total synthesis of capanelle via 1,3 propargyl acetate shift/Nazarov cyclization/cyclopropanation cascade by Malacria*

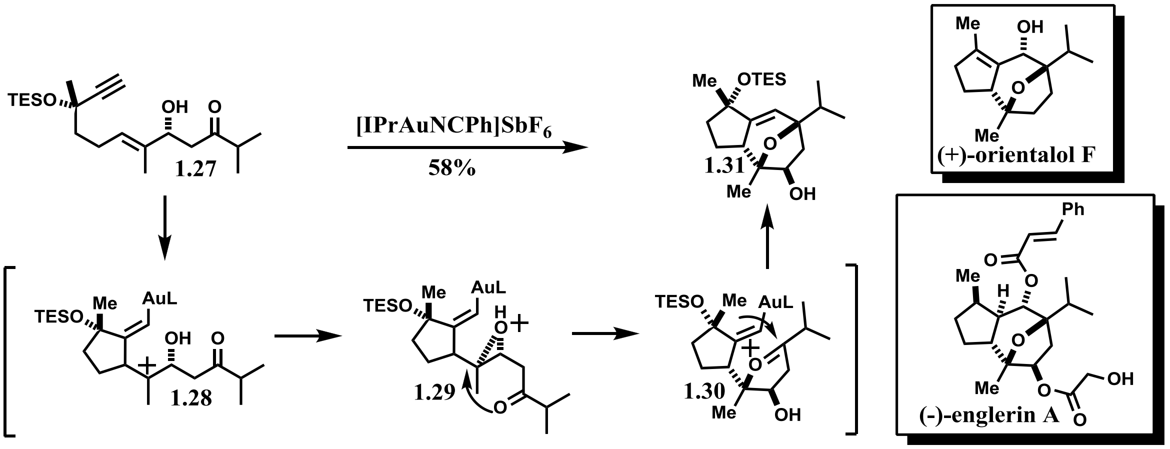
Propargyl acetates also can be mild synthetic alternatives to diazo compounds and participate in a cyclopropanation reaction. Professor Nevado developed an enantioselective intermolecular cyclopropanation of vinyl gold carbenoid (**1.24)**, which was the result of a gold-catalyzed 1,2 acetate shift of propargyl pivaloate (**1.22)**, followed by a homo-Cope rearrangement.[13] After in situ hydrolysis and equilibration, the thermodynamically favored ketone (**1.26**) could be isolated in 68% yield and over 90% ee. Cycloheptenone (**1.26**) is an advanced intermediate in the formal enantioselective synthesis of frondosins A**.**



Scheme 1.06 *Total synthesis of frondosin A via 1,2propagyl acetate shift/ intermolecular cyclopropanation/homo-Cope rearrangement by Nevado*

Echavarren, a pioneering researcher in gold(I)-catalyzed cycloisomerizations of enynes, used a pendant carbonyl to a 1,6-enyne to trap the cationic intermediate (**1.28**) generated after the first carbon–carbon bond. The addition of the oxygen to the tertiary carbocation (**1.28**) led to cyclic oxocarbenium (**1.30**), which underwent a Prins type cylization to afford oxatricycle (**1.31**) containing a bridged furan ring. This formal [3+2] dipolar cycloaddition built the tricyclic core during the enantioselective synthesis of englerin A and orientalol F.[14] Ma's group reported the same key step for the synthesis of englerin A.[15] Its substrate was analogous to enyne (**1.27**) without the protected tertiary alcohol.

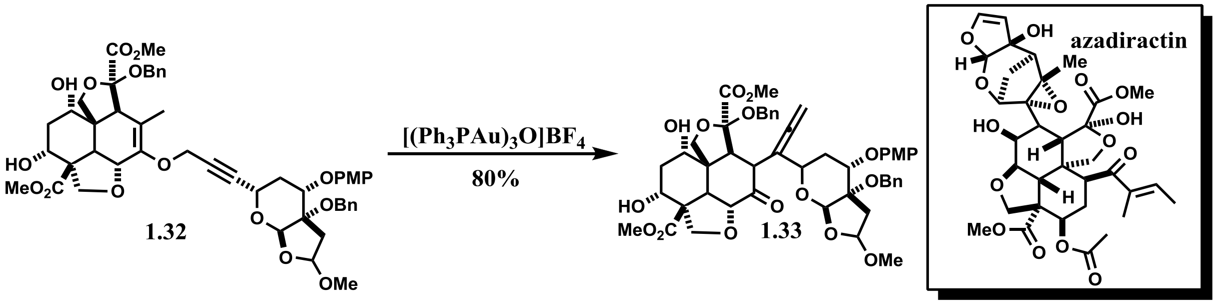
These studies revealed the synthetic importance of this functional group. Substrate (**1.27**) undergoes a more selective and efficient gold catalyzed process and the resulting tertiary alcohol in tricycle (**1.31**) furnishes a good synthetic handle to finish the synthesis of both natural products.



Scheme 1.07 *Total synthesis of (-)-englerin A via 1,6-enyne cycloisomerization/Prins type cyclization cascade by Echavarren*

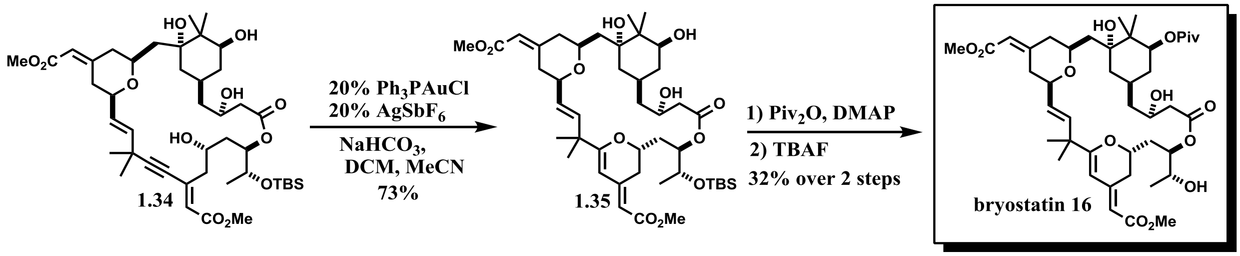
1.5 Highly chemoselective Lewis acid π-activation of alkyne

The last examples are mechanistically less complex, but the chemoselectivities encountered are of paramount importance for the transformation of such advanced intermediates that are surrounded by a high density of functional groups. The high chemoselectivity not only allows selective transformation of complex molecules containing various functional groups, but also reduces the use of multiple protecting groups. A Claisen rearrangement was used to merge two fully functionalized units for the total synthesis of azadiractin.[16] The Claisen rearrangement of propargylic enol ether (**1.32)** could be achieved thermally, under microwave irradiation, at 185 °C, but the notably mild conditions render the gold catalyzed method much more robust and attractive in preparative terms.



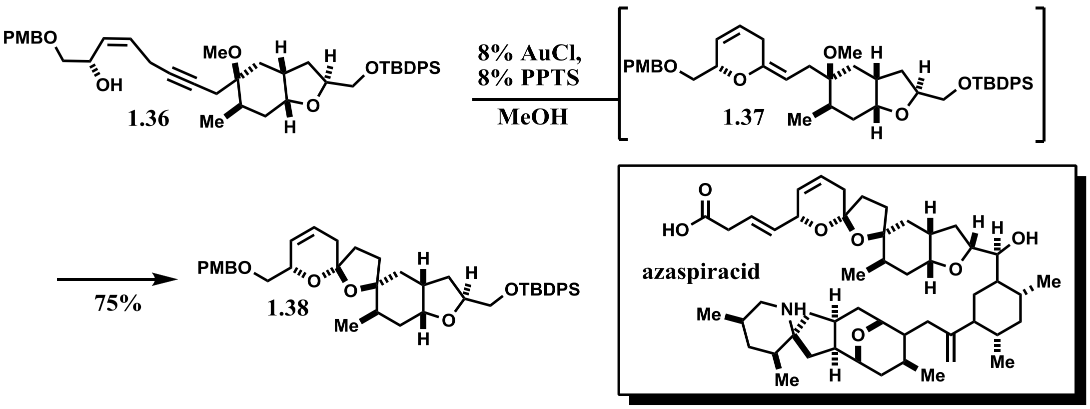
Scheme 1.08 *Total synthesis of azadiractin via 3,3 sigmatropic rearrangement by Ley*

The total synthesis of bryostatin 16 by Trost and his coworkers provides more evidence of the high chemoselectivity which can be achieved via gold catalysis.[17] Despite the gold-catalyzed step being late in the synthesis and the fact that macrocycle (**1.34**) is crowded with oxygen functionalities and unsaturated moieties, only one protecting group is needed. Since the product (**1.35**) is highly sensitive to acid, the selective 6-*endo*-*dig* cyclization, which forms the C ring of bryostatin 16, is accomplished in a buffered solution allowing the isolation of sensitive macrocycle (**1.35**) in good yield.



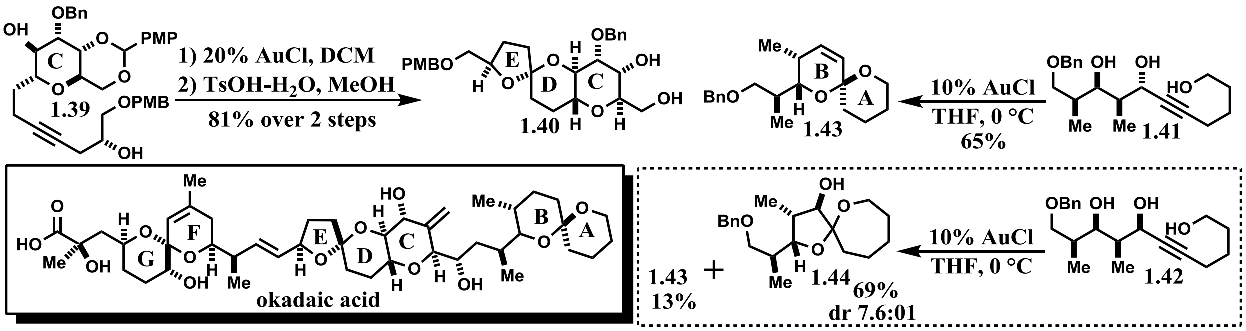
Scheme 1.09 *Total synthesis of bryostatin 16 via 6-endo-dig gold(I)-catalyzed hydroalkoxycyclization by Trost*

Transformations that form polycyclic furans and pyrans play an important role in total synthesis, as these motifs are frequently found in biologically active natural products.[18] As seen in **Scheme 1.09**, after the initial carbon-oxygen bond, an enol moiety is obtained. Under acidic conditions another heterocyclization can happen, and thus an alkyne can be synthetically equivalent to a ketone in a spiroketalization process. The use of robust alkynes brings unambiguous synthetic advantages: first, as an easy modular disconnection and, second, as a way to avoid the need for protection and activation, which are strategies typically encountered in carbonyl chemistry. During the formal synthesis of azaspiracid, the use of an alkyne in (**1.36**) instead of a ketone as the precursor for the ketal functionality eliminates the risk of alkene isomerization and/or conjugation.[19] After a 6-*exo*-*dig* heterocyclization to furnish cyclic enol (**1.37**), an acid-promoted spiroketalization, followed by the loss of dimethyl ether, afforded the desired tetracyclic core (**1.38**). The diastereoselectivity in the ketal formation is based on thermodynamic control.



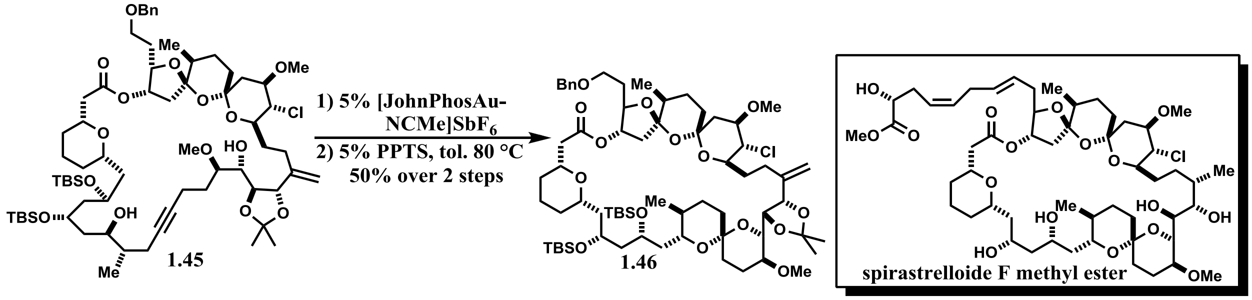
Scheme 1.10 *Total synthesis of azaspiracid via gold(I)-catalyzed spiroketalization by Forsyth*

The gold-catalyzed additions of oxygen nucleophiles to carbon–carbon multiple bonds is a significant synthetic strategy for generating polyheterocycles, in particular cyclic spiroketals. Even two gold-catalyzed spiroketalizations were applied as key steps in the formal total synthesis of okadaic acid (**Scheme 1.11**).[20] Cyclic ether (**1.39**) enables the formation of 5,6-membered ring spiroketal (**E-D**), while linear precursor (**1.41**) allowed selective formation of the 6,6-membered ring spiroketal (**A-B**). For cyclic ether (**1.39**), even under acid-free conditions, parts of the anisylidene group were deprotected. But, the *in situ* cleavage, based on the Lewis acidity of the gold catalyst, had no negative effect on the catalysis and subsequent full deprotection with additional tosic acid furnishes spiroketal (**1.40)** in good yield. For the second ketal precursor, 1,3-*anti*- and 1,3-*syn*-triols (**1.41**) and (**1.42**) were obtained as epimers during their synthesis and both of them were subjected to the gold catalyst. The relative configuration was found to be important for the selectivity of the reaction. While the *anti*-triol (**1.41**) delivered the desired spiroketal (**1.43**) as the exclusive product, three different products were obtained in the case of *syn*-diol (**1.42**). For this precursor, the major pathway derived from an initial 5-*exo*-*dig* cyclization and both epimers of the spiroketal (**1.44**) were obtained in a ratio of 7.6:1.



Scheme 1.11 *Formal synthesis of okadaic acid via gold(I)-catalyzed spiroketalization by Forsyth*

The most recent application of spiroketalization in a highly complex environment was presented by the Fürstner group during its synthesis of the antimitotic macrolide Spirastrellolide F methyl ester.[21] After macrocyclization via an alkyne metathesis to access compound (**1.45**), a two-step procedure allows formation of the second spiroketal moiety of the desired compound and delivers, in 50% yield, the macrocycle (**1.46**). Like the gold-catalyzed step of the azaspiracid synthesis (**Scheme 1.10**), addition of acid and heating were necessary for the addition of the sterically-hindered secondary alcohol. Interestingly, in this case, a Buchwald-type ligand was the best choice for addressing the desired selectivity in the gold catalyzed heterocyclization.



Scheme 1.12 *Total synthesis of spirastrelloide F methyl ester via a gold(I)-catalyzed carbocyclization by Fürstner*

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Chapter 2

Polycyclic Polyprenylated Acylphloroglucinols

2.1 Introduction to PPAPs: chemical structures and biological activities

Polyprenylated polycyclic acylphloroglucineols (PPAPs) are a large family of natural products, which includes more than 200 members that have been discovered to date. Most of these compounds were isolated from plants and trees from Clusiaceae (Guttiferae), a family of plants that includes more than 37 genera and 1600 species.[1] This family of natural products possesses a wide range of biological activities like antibiotic, antiseptic, anti-HIV, anti-inflammatory, anti-neurodegenerative, antioxidant, anticancer or antidepressant properties.[2] Although few bicyclo[3.2.1]octane-2,4,8-trione central core are found like enaiemone B (**2.11**) and ialibinone A (**2.12**), most of these compounds have highly oxygenated and densely functionalized bicyclo[3.3.1]nonane-2,4,9-trione core.

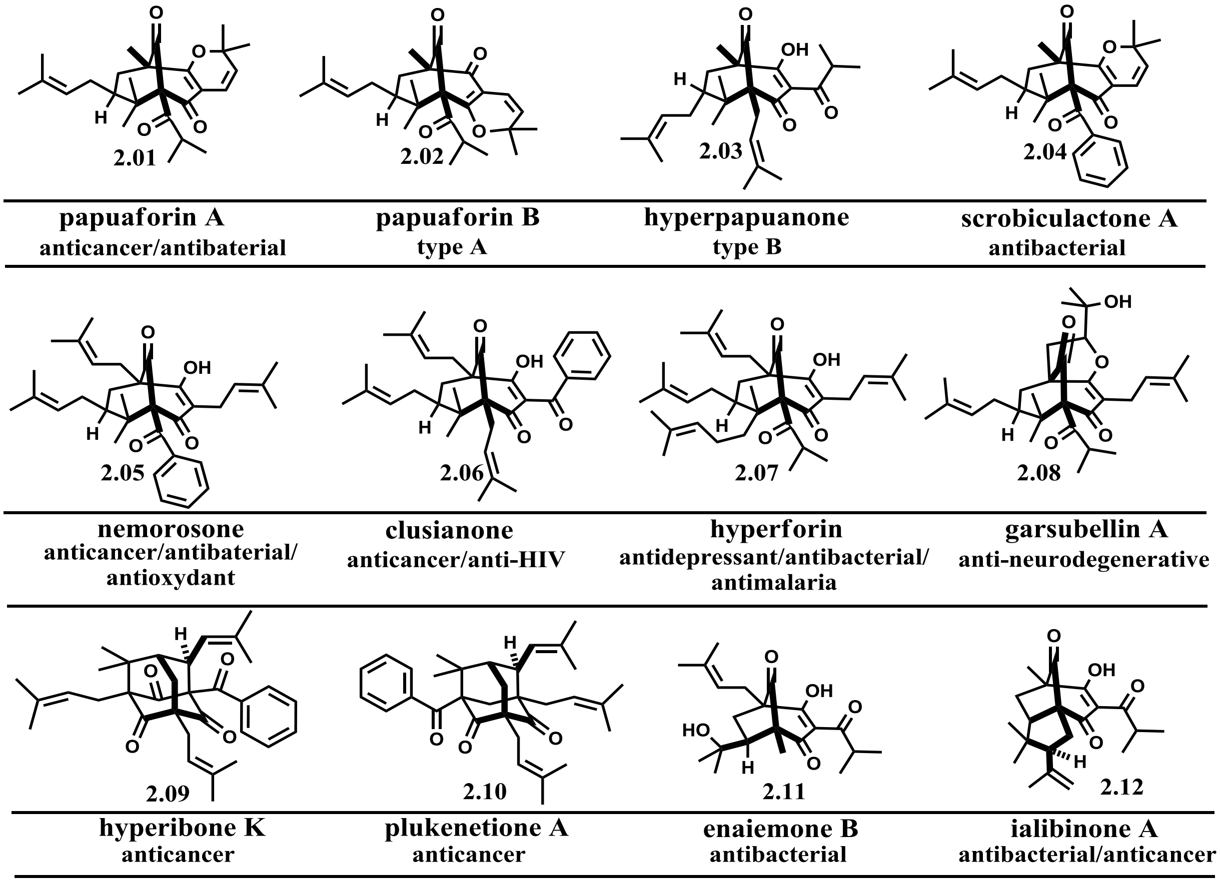
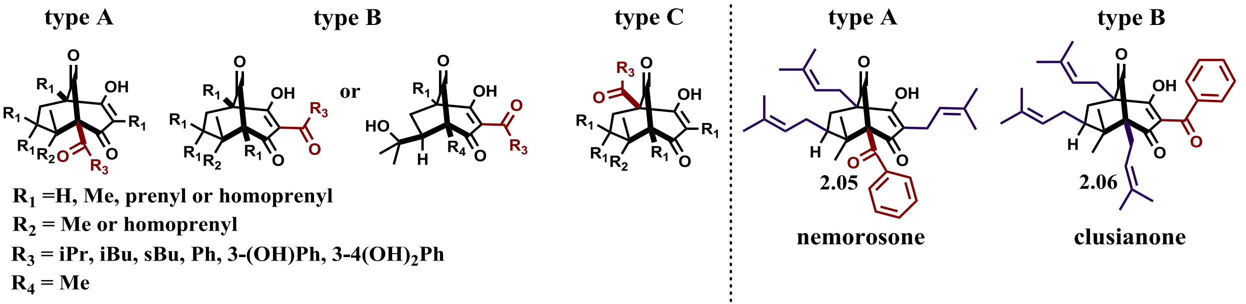


Figure 2.01 *Structures of selected PPAPs along with their reported biological activities*

The bicycle framework is usually decorated with prenyl, geranyl and acyl side chains. In some of these compounds further cyclization takes place between the ß-diketone and the pendant olefinic groups, forming secondary ring systems on the bicyclic core and leading to adamantanes, dihydrofurano or pyrano-fused cyclic substructures as found in compounds (**2.01, 2.02, 2.03, 2.08, 2.09, 2.10** and **2.12)**. Hyperibone K (**2.09**) and its regioisomer pluketione A (**2.10**) are examples of rare adamantane-containing natural products.[3]

Based on the position of the acyl group relative to the quaternary center on the bicyclic core and on the proposed biosynthesis, the members of the PPAP family have been categorized into three classes: type A, type B and type C. Type A structures, exemplified by nemorosone (**2.05**), are the most common and comprise more than a hundred known structures. This family bears the acyl group at the bridgehead position adjacent to the quaternary centers. Type B compounds, such as clusianone (**2.06**), are approximately half as prevalent as those of type A and the acyl group is located at the α-position to the β-hydoxyenone. Type C structures are the least common and bear the acyl group at the opposite bridgehead position relative to the quaternary center (**Figure 2.02**). The question if the structure of type C has been correctly determined is still under debate.[4] After all, this type of PPAP does not derive from the same biosynthetic intermediate as type A and B. Their broad biological activities combined with their unique and challenging structural features have made some of these molecules a prestigious target in the field of total synthesis of complex natural products.



R_1 =H, Me, prenyl or homoprenyl
R_2 = Me or homoprenyl
R_3 = iPr, iBu, sBu, Ph, 3-(OH)Ph, 3-4(OH)$_2$Ph
R_4 = Me

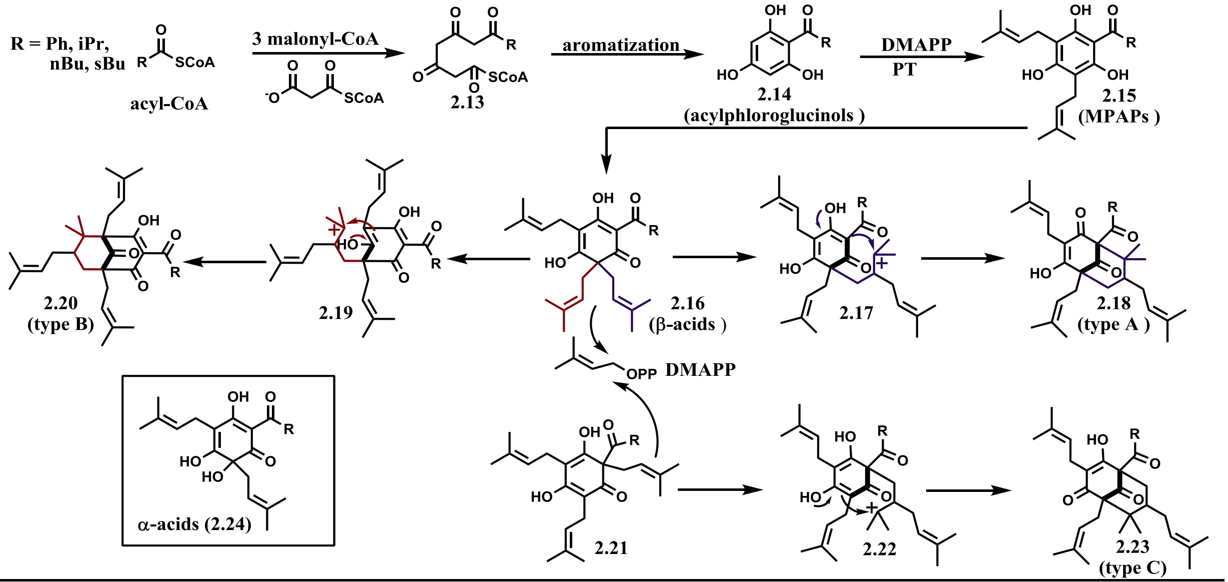
Figure 2.02 *Type A, B, C PPAPs*

St John's wort (*Hypericum perforatum* extracts) was used by the ancient Greeks as a remedy for many skin injuries, burns and neuralgia.[5] These herbal extracts are currently used in some countries for the treatment of mild depression, anxiety, and sleep disorders, especially for children. Hyperforin (**2.07**), the active ingredient in St-John's wort, is also known for its antibacterial properties and has recently been a promising candidate for the treatment of cancer.[6]

Another important target of the type A scaffold is garsubellin A (**2.08**), a natural product noted for its activities against neurodegenerative diseases. In fact, recent studies have shown that garsubellin A (**2.08**) induces the biosynthesis of acetylcholine, a neurotransmitter that, at low concentrations, can lead to Alzheimer's disease.[7] Simple PPAPs are also interesting, such as nemorosone (**2.05**), which exhibits antimicrobial, cytotoxic, and antioxidant activities, while clusianone (**2.06**) a type B PPAP, is known for its anti-HIV activity.[8]

2.2 Biosynthesis of PPAPs

PPAPs are biosynthetically derived from less complex monocyclic polyprenylated acylphloroglucinols (MPAPs) (**2.15**), which are found in many plants from the Myrtaceae and Cannabinaceae families. MPAPs are reported to show antimicrobial, antifungal, and antifeedant activity.[9] MPAPs are derivatives of acylphloroglucinols (**2.14**) which contain an acyl group and two or three 3-methyl-2-butenyl (prenyl) side chains. The acylphloroglucinol moiety could be constructed biosynthetically via a polyketide pathway, with the attachment of one acyl-CoA group and three malonyl-CoA groups to furnish polyketide (**2.13**).[10] An enzyme-assisted Dieckmann condensation and aromatization produce acylphloroglucinols derivatives (**2.14**).



Scheme 2.01 *Biosynthesis of type A, B and C PPAPs*

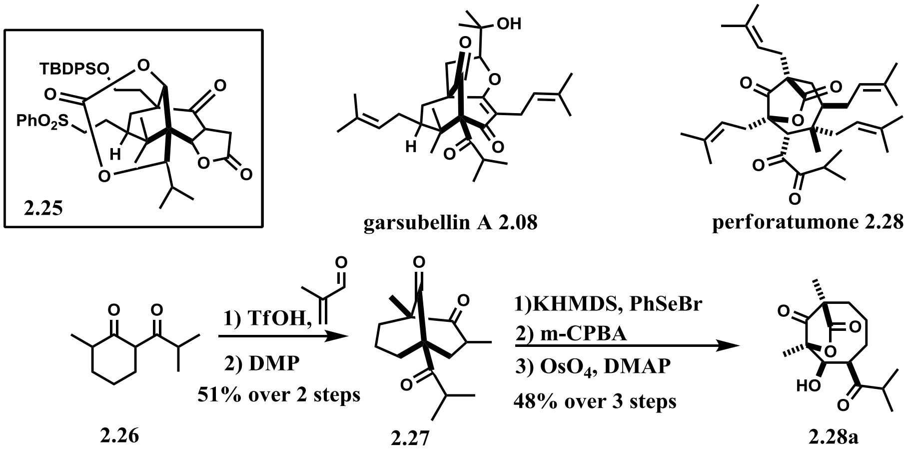
Further electrophilic substitution reactions on acylphloroglucinol moiety with dimethylallyl diphosphate (DMAPP), involving prenyltransferase enzyme, result in the formation of acylphloroglucinol MPAPs (**2.15**) and later in β-acids precursors (**2.16**). Cuesta-Rubio proposed a mechanism for the cyclization of MPAPs to type A and type B PPAPs via a common β-acids intermediate (**2.16**).[11] The dimethylallyl pyrophosphate (DMAPP) make a carbon-carbon bond with one prenyl unit of the geminal diprenyl groups of the β-acids, resulting in one of two stable tertiary carbocation intermediates (**2.17)** and (**2.19**). Addition of the C1 enol moiety on the carbocation (**2.17**) would give type A PPAPs (**2.18**) and the addition of the C5 enol would result in type B PPAPs (**2.19**). Type C PPAPs may be made biosynthetically from a different set of MPAPs (**2.21**) having a quaternary center attached to the acyl group instead of a prenyl group. Reaction with prenyl pyrophosphate (DMAPP) will lead to a tertiary carbocation intermediate (**2.22**) and the resulting addition of C3 from the cationic intermediate would result in type C PPAP (**2.23**). Interestingly, MPAPs are an α-acid (**2.15**) and are converted during the brewing process into an iso-α-acids (**2.24**), the compound that is responsible for the flavor and bitter taste of beer.[12]

2.3 Previous synthetic works towards PPAP

The complex molecular framework of PPAPs, combined with their promising therapeutic potential has drawn attention from several research groups**.**[**2**] Many groups, including our own, have succeeded in completing the total synthesis of several PPAPs. Considering the enormous work done in the scientific community to this end, and the fact that most strategies and methodologies developed for the construction of the bicycle[3.3.1]nonane system have been reviewed, only landmark examples highlighting the progressive achievements toward this large family of natural products will be presented.[13]

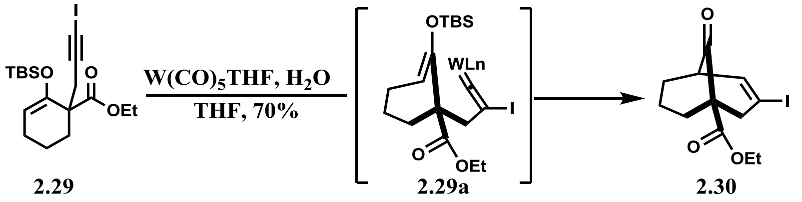
In 1999, Professor K. C. Nicolaou and his team were the first group to report a synthetic route towards garsubellin A (**2.08**) employing a selenocyclization approach (**Scheme 2.02**).[14] This first route counts 24 synthetic steps and lead to an advanced intermediate (**2.25**). At first glance, this intermediate seemed more complex than the natural product targeted, however, all the necessary synthetic handles to complete the synthesis were installed. No further reports using this strategy have been reported to date. In 2005, Nicolaou and co-workers disclosed an acid-catalyzed Michael/Aldol sequence to rapidly access the bicyclic scaffold of PPAPs and cogeners.[15] Treatment of cyclic β-ketoester (**2.26**) and methacrolein with triflic acid afforded the annulation product as a mixture of diastereoisiomers, both of which could be converted into bridged triketone (**2.27)** as a single diastereoisomer in the subsequent oxidation step using -

Dess Martin periodinane (DMP). This process gives an overall yield of 51% over two steps and allowed the simultaneous generation of the two bridgehead quaternary centers. Treatment of the bicyclic triketone (**2.27)** with KHMDS and phenylselenide bromide, followed by oxidation with m-CBPA and subsequent elimination, gave an enone which was readily converted into an eight-membered ring lactam (**2.28**). This interesting rearrangement is mediated by an OsO_4 dihydroxylation and the resulting scaffold is found in some natural products such as perforatumone (**2.28**).[15b]



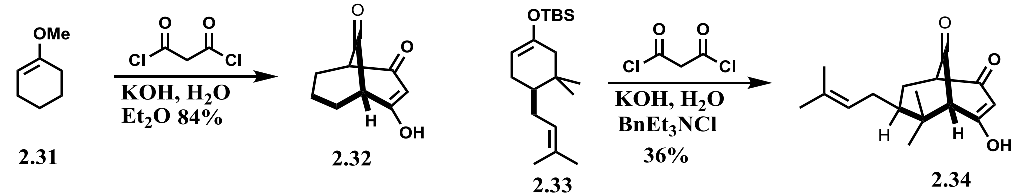
Scheme 2.02 *Nicolaou's intermediate and Michael/aldol/ring expansion oxydation strategy*

In 2001, Iwasawa published an interesting tungsten-catalyzed *6-endo-dig* carbocyclisation between a silyl enol ether and a substituted alkyne to access the bridged bicyclic ketone (**2.30)** in 70% yield.[16] This transformation passes through a vinylidene intermediate (**2.29a**), limiting the substitution of the alkyne to iodide and hydrogen. This work was not relevant for its synthetic access to PPAPs, but was an important foundation for our work described herein. As this work is closely related to ours, the mechanism will be discussed in greater detail in the following chapter.



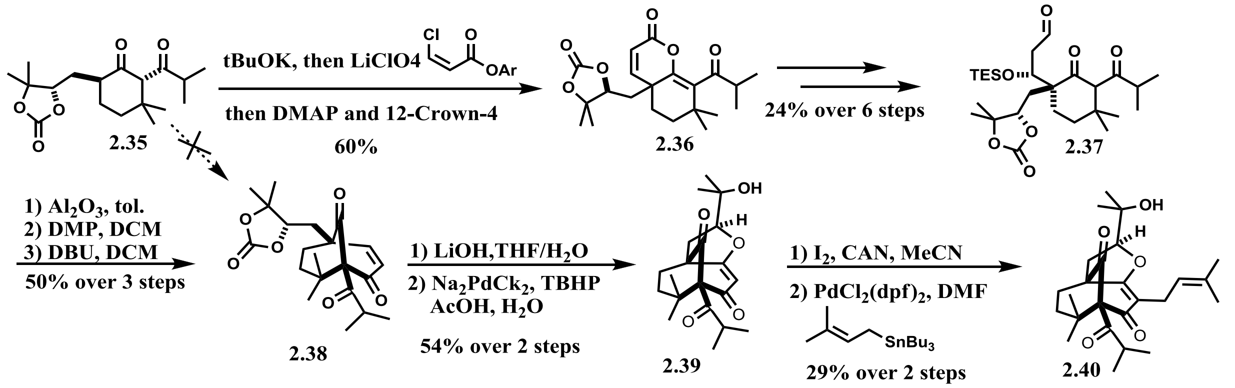
Scheme 2.03 *Iwasawa's methodology: tungsten-catalyzed 6-endo-dig carbocyclization*

The first tandem bond forming disconnection was reported by the Stoltz's group, employing an Effenberger cyclization (**Scheme 2.04**).[17] This strategy has become one of the most popular approaches for this class of molecules and some total syntheses using this strategy will be discussed in the next section. Stolz et al. demonstrated that it was possible to form the bicyclic skeleton (**2.32**) in 84% yield using an excess of enol ether (**2.31**) with malonyl dichloride as the limiting reactant. In order to access PPAPs, an excess of valuable enol ether (**2.33**) was not favorable and therefore they modified the procedure to use only one equivalent of enol ether (**2.33)**. It is important to underline that, even the intermediate (**2.33)** does not possess the bridgehead substituent, the bicyclo[3.3.1]nonane **(2.34)** core was only isolated in a modest yield of 36%. Interestingly, the cyclisation was diastereoselective and only the *anti*-isomer at the prenyl side chain was formed, which turned out to be real synthetic advantage for the construction of PPAPs. The lower yield shows that the cyclization is more difficult when the *gem*-dimethyl moiety is present on the enol ether ring (**2.33→2.34**)



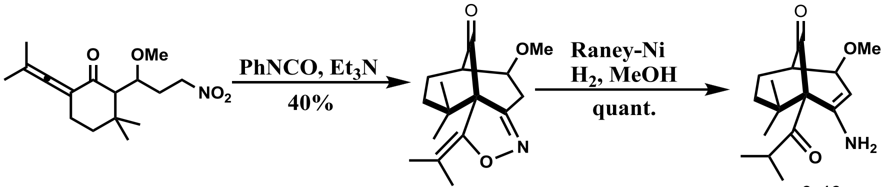
Scheme 2.04 *Stoltz's approach: the Effenberger cyclization*

In 2002, Shibasaki and co-workers reported synthetic studies towards the synthesis of naturally occurring PPAPs (**Scheme 2.05**).[18] Their approach utilized a one-pot Michael addition-elimination between 1,3-diketone (**2.35)** and *cis*-chloroacrylate, which did not give the desired bicycle (**2.38)**, but instead the bicyclic lactone (**2.36**). [18a,b] A subsequent sequence of six steps afforded the aldehyde (**2.37**), which was further transformed into the desired bicyclic compound (**2.38**). An aluminum(III)-mediated aldol cyclization followed by an oxidation and a subsequent elimination furnished enone (**2.38**). Deprotection of the diol and a Wacker type cyclization provides the tricyclic furan (**2.39**). The advanced intermediate (**2.40**) was obtained from a Stille coupling and was only missing one prenyl side chain.



Scheme 2.05 *Shibasaki's approach: Michael/Dieckman/aldol strategy*

The construction of PPAPs framework using an intramolecular [3+2] cycloaddition between an allene and a nitrile oxide was reported by Young and co-workers (**Scheme 2.06**).[19] Treatment of compound (**2.41**) with phenyl isocyanate and triethylamine induces the cycloaddition and created the bridged bicylic framework. The synthesis was further carried out by reductive cleavage of the isoxazoline (**2.42**) to afford enamine (**2.43**).



2.41 **2.42** **2.43**

Scheme 2.06 *Young's approach: an allene-nitrile oxyde [3+2] cycloaddition*

George Kraus and his group published three distinct strategies to quickly access the bicyclo[3.3.1]nonane core (**Scheme 2.07**).[20] In 2003, they showed that it is possible to make the bridged bicyclic ring system using a manganese-mediated oxidative free radical cyclization. A simple β-keto ester (**2.44**) was converted into bicycloalkene (**2.45**) via an intramolecular *6-endo-trig* carbocyclisation using manganese acetate and copper acetate. Treatment of bicycloalkene (**2.45**) with NBS led to the dibromide intermediate (**2.46**). Further addition of NBS gave a tribromide intermediate which was transformed into bromoenone (**2.47**) in the presence of aqueous acetic acid at 115 °C. In 2005, they employed an addition-elimination strategy using diacetoxyvinyl sulfone as a double Michael acceptor to form the bicyclic ring system (**2.49**). A subsequent treatment of bicycloalkane (**2.49**) with sodium amalgam gave compound (**2.50**). In 2008, Kraus reported an original strategy to access an advanced intermediate towards the synthesis of papuaforin A (**2.01**). The key bonds were made by a Michael addition of methyl acrylate to β-ketoester (**2.51**) followed by a Birch reduction cyclization to afford bicyclic diol (**2.52**) in 85% yield. The diol (**2.52**) was oxidized and the resulting diketone was readily converted to the corresponding silyl enol ether. The latter was treated with NBS in refluxing carbon tetrachloride to furnish α-bromoenone (**2.53**) which, after two steps, was converted to hemiacetal (**2.54**). The last compound (**2.54**) is the most advanced intermediate towards the synthesis of papuaforin A published by this group (**2.01**)

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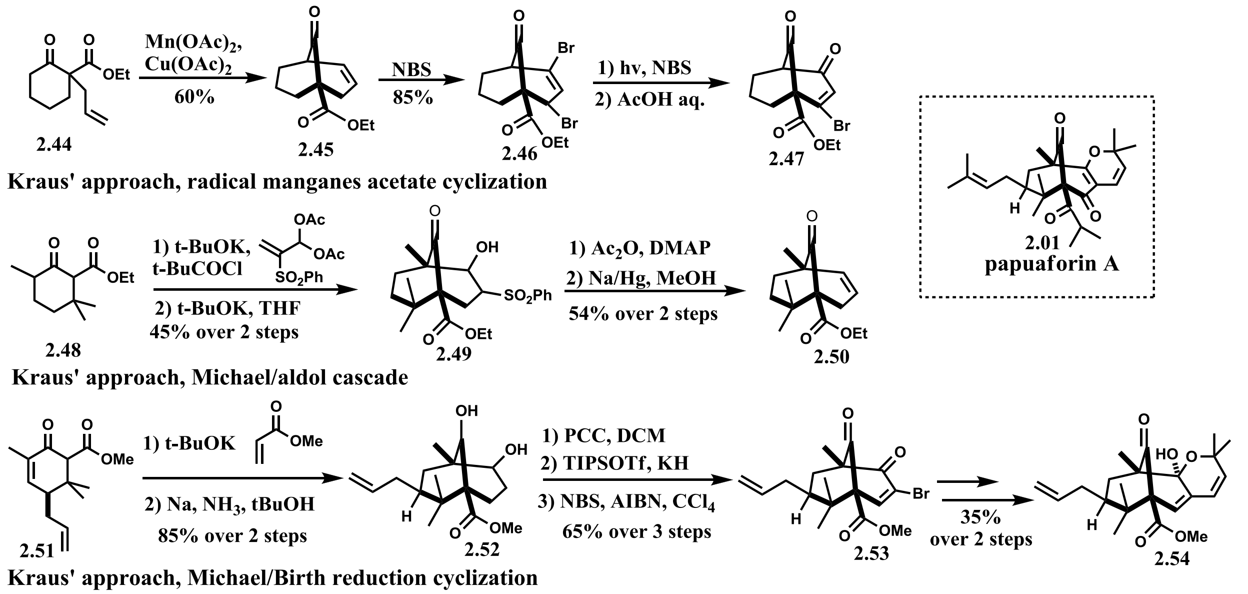
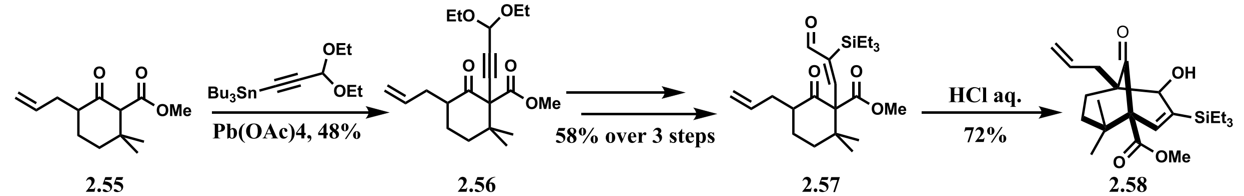


Scheme 2.07 *Overview of Kraus'approaches*

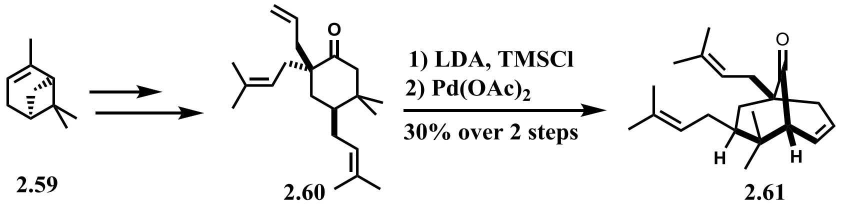
In 2003, Grossman et al. reported the construction of the bicyclo[3.3.1]nonane ring core of PPAPs (**2.58**) via an intramolecular aldol reaction of *cis*-enal (**2.57**).[21] The bridged bicyclic ring precursor (**2.57**) was prepared via a four steps sequence. First, a reaction of alkynylation between β-ketoester (**2.55**) and alkynyltributyltin in the presence of Pb(OAc)4 gave compound (**2.56**). An acid-mediated acetal deprotection of acetal (**2.56**) followed by a *syn* hydrosilylation using Co2(CO)6 complex produced *E*-α-silyl enealdehyde (**2.57**). Finally, an acid-mediated aldol-cylisation provided the bridged bicycle (**2.58**).



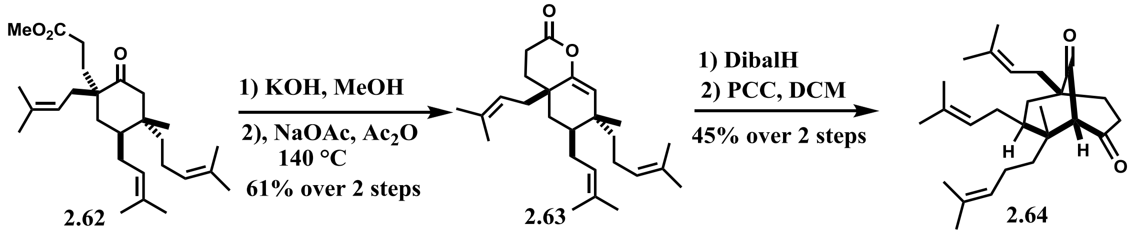
Scheme 2.08 *Grossman's approach: the alkynylation/aldol strategy*

Mehta and coworkers investigated four different strategies for the formation of bicyclo[3.3.1]nonane core, however only two approaches will be highlighted.[22] Initially, they were using a palladium(II)-catalyzed Kende cyclisation. Starting from α-pinene (**2.59**), this approach was the first reported enantiospecific synthesis of a fully advanced intermediate of a PPAP family member. In subsequent work, Mehta and co-workers used a DIBAL-H mediated reduction of a ring fused lactone (**2.63**) to initiate a thermodynamically-controlled retro-aldol aldol cascade to generate the advanced bicyclic intermediate (**2.64**) in 45% over two steps.

In order to access an higher oxidation state bridged bicycle, Metha also investigated the Effenberger cyclization. [22d]



Mehta's approach: a palladium-catalyzed Kende Cyclization



Mehta's approach: a DIBAL-H mediated retro-aldol/aldol cyclization

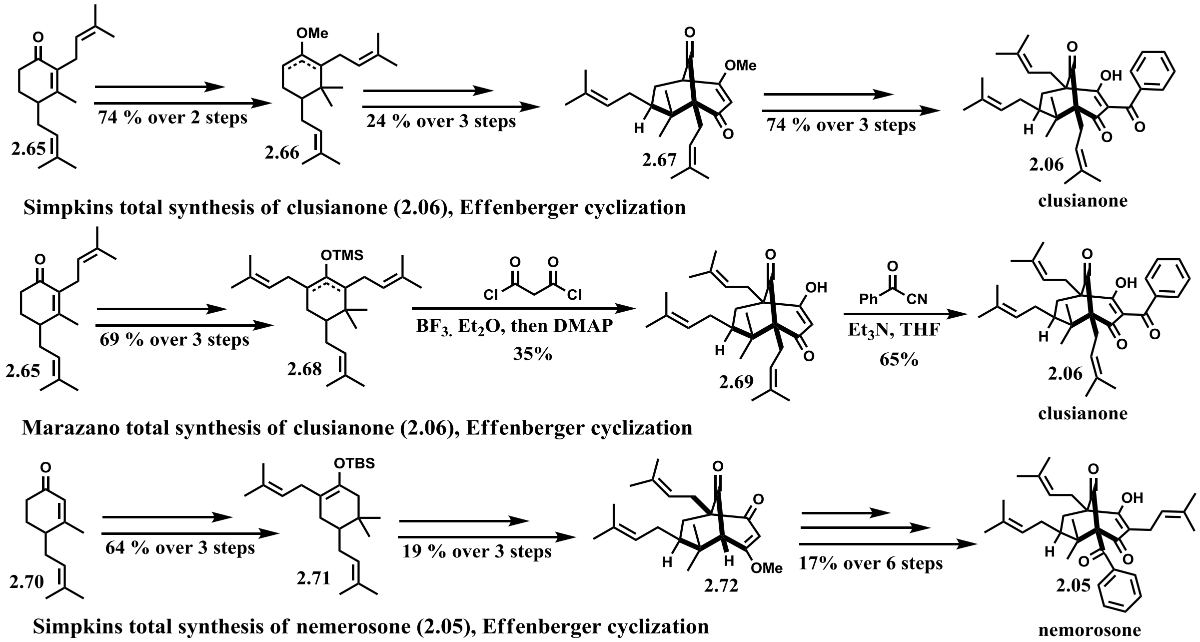
Scheme 2.09 *Overview of Mehta's approaches*

2.4 Total synthesis of PPAPs

A decade after Nicolaou had reported the synthesis of the first fully functionalized advanced synthetic intermediate (**2.25**), five research groups have succeeded in synthesizing only three PPAPs. Early efforts relied on the formal annulation of a three-carbon bridge onto a polyfunctionalized cyclohexanone derivative to afford the bicyclic framework. The highly oxygenated framework and the two bridgehead quaternary carbons revealed some difficulties in using this linear and modular strategy. Long and tedious functional group manipulations are often needed to access these complex bicyclic frameworks from an over-simplified model system and the adjustment of the desired oxidation state can be long-winded. However, the latest versions of this strategy appear promising, while recent efforts have decreased the number of steps compared to earlier attempts. Moreover, this synthetic strategy offer the opportunity to further incorporate almost any side chain that may be required, at any position, in order to access a variety of analogues using the same approach. The second general strategy is the alkylative dearomatization of substituted phenols. At first glance, this strategy appears more attractive as higher overall yields are observed and as this approach is closely related to the natural pathway. Furthermore, the biomimetic dearomatization strategy could take advantage of the hidden symmetry within the targeted molecule to drastically shorten the number of synthetic steps. The only issue is that these convergent syntheses are more limited in the number of different analogues easily accessible with the same synthetic strategy. However, recent developments have allowed the synthesis of more members of the family and the challenging structure of hyperforin (**2.07**) has been made successfully twice already. The target that initially captured the attention of the synthetic community was garsubellin A (**2.08**), independently attained in 2005 by the groups of professor Shibasaki and professor Danishefsky.[18c,25a] A year later, the group of Simpkins reported a formal synthesis using the popularized Effenberger cyclization. In the following years, nemorosone (**2.05**), clusianone (**2.06**) and hyperforin (**2.07**) emerged as popular synthetic targets; clusianone (**2.06**) is at the top of the list with seven syntheses reported. In this section, we will cover almost all the total syntheses published to date with the exception of those of garsubellin A (**2.08**).

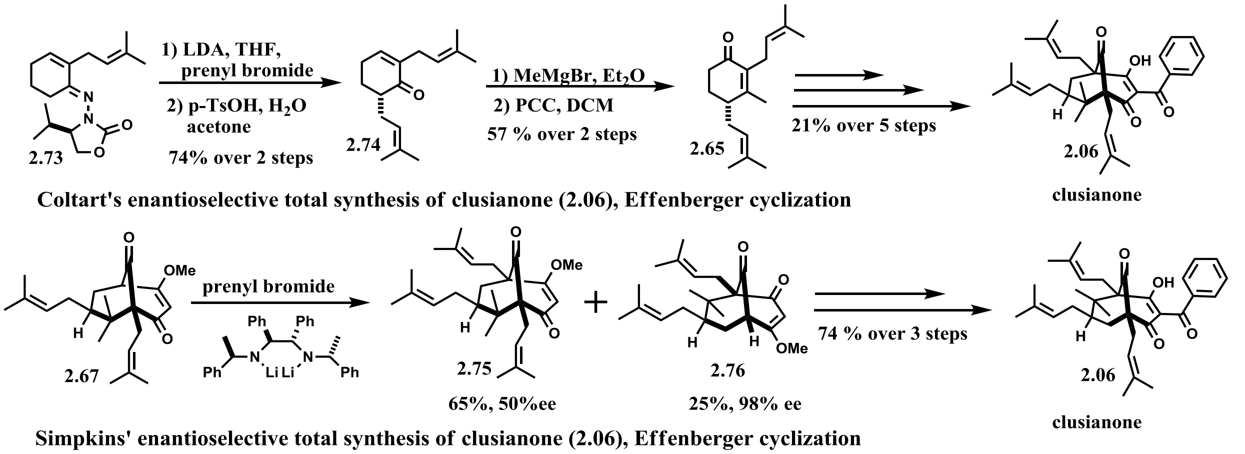
2.5 Total synthesis of PPAPs: first synthetic strategy

After the landmark study by Stolz, the Effenberger cyclization became one of the most popular strategies to access PPAP natural products.[23] Three different groups have reported the synthesis of clusianone using this method. Simpkins was the most active researcher in this field and report the synthesis of nemorose (**2.05**) as well as an enansioselective synthesis of clusianone (**2.06**).[23a,b] Each group started their synthesis with a sequence originally developed by Stork and Danheiser to access cylohexenone (**2.65**) or (**2.70**).[24]



Scheme 2.10 *Resume of Effenberger cyclization for the total synthesis of clusianone (**2.06**) and nemorosone (**2.05**)*

After the formation of corresponding silyl enol ether (**2.66**), **2.68**) or (**2.71**), the key Effenberger cyclization with malonyl dichloride was performed. Marazano reported the shortest synthesis and the only annelation with prenyl substituents at both bridgehead carbons, which led to bicycle (**2.69**).[23c] For the others, functionalization of the second bridgehead carbon was performed after the formation of the bicyclo[3.3.1]nonanone core. Enantioselective syntheses of PPAPs had also been reported using the Effenberger cyclization strategy (**Scheme 2.11**). While Simpkins developed a late asymmetric prenylation of the advanced intermediate (**2.67**), Coltart employed an asymmetric α-alkylation of chiral cyclic *N*-aminocarbamate derived hydrazones (**2.73**) to install the prenyl unit.[23e,f]

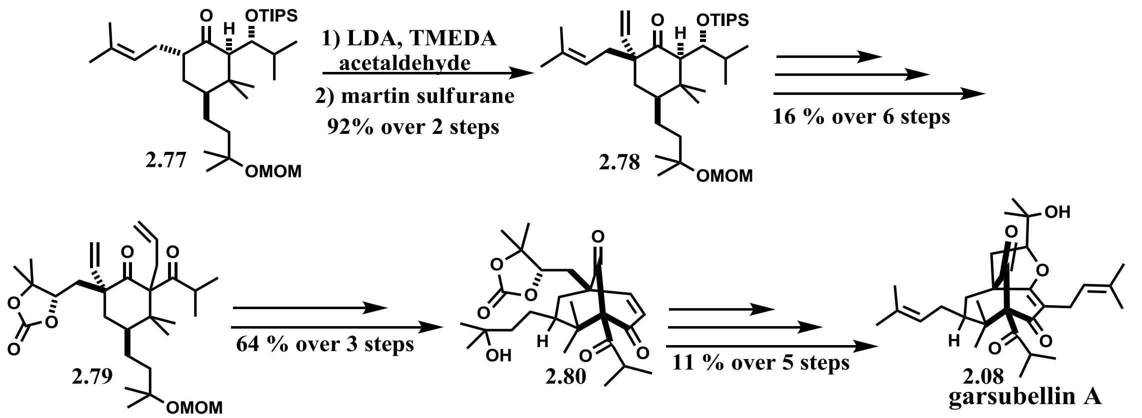


Coltart's enantioselective total synthesis of clusianone (2.06), Effenberger cyclization

Simpkins' enantioselective total synthesis of clusianone (2.06), Effenberger cyclization

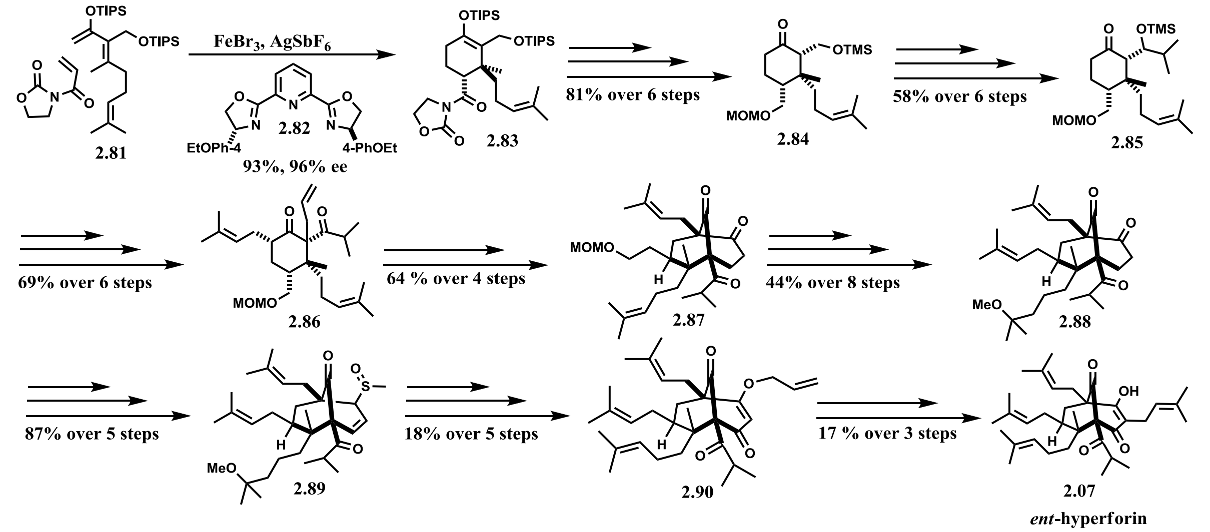
Scheme 2.11 *Overview of the successful Effenberger cyclization for the enantioselective total synthesis of clusianone (**2.06**)*

Professor Shibasaki has been one of the most prolific contributors in this area, with the synthesis of the two most challenging targets, garsubellin A (**2.08**) and hyperforin (**2.07**) (**Scheme 2.12** and **2.13**).[18c,e] While the publication of both syntheses was a landmark in the field of PPAP synthesis, Shibasaki's syntheses highlights the difficulties in constructing such polysubstituted cyclohexanone, in particular due to the necessary substitution of both bridgeheads, and due to the robustness of the annelation method required to tolerate a sterically hindered environment. In the case of garsubellin A (**2.08**), a fifteen step sequence was necessary to access diene (**2.79**), which upon treatment with 2nd generation Hoveyda-Grubbs catalyst, gave the corresponding bridgehead ketone.[18c] A subsequent allylic oxidation using Barton's selenium oxidation procedure and followed by a deprotection of the MOM-ether afforded cyclohexenone (**2.80**). This advanced intermediate (**2.80**) was converted to garsubellin A (**2.08**) in five further steps in 11% overall yield.



Scheme 2.12 *Ring closing metathesis for the total synthesis of garsubellin A (**2.08**) by Shibasaki*

Nearly thirty years after its initial isolation, a fifty step asymmetric synthesis of hyperforin (**2.07**) was disclosed by Shibasaki (**Scheme 2.13**).[18e] The synthesis began with an asymmetric Diels–Alder reaction between silyl enol ether (**2.81**) and oxazolidinone acrylamide, promoted by cationic iron–pybox complex (**2.82**), to afford polysubstituted cyclohexane (**2.83**) in excellent yield and enantiomeric excess (93%, 96% e.e.). The latter compound was converted to cyclohexanone (**2.84**) after a series of functional group manipulations and protections. Despite the lengthy synthetic sequence that merely introduced an additional isopropyl group, the six step transformation of (**2.84**) to (**2.85**) proceeded with 58% overall yield.

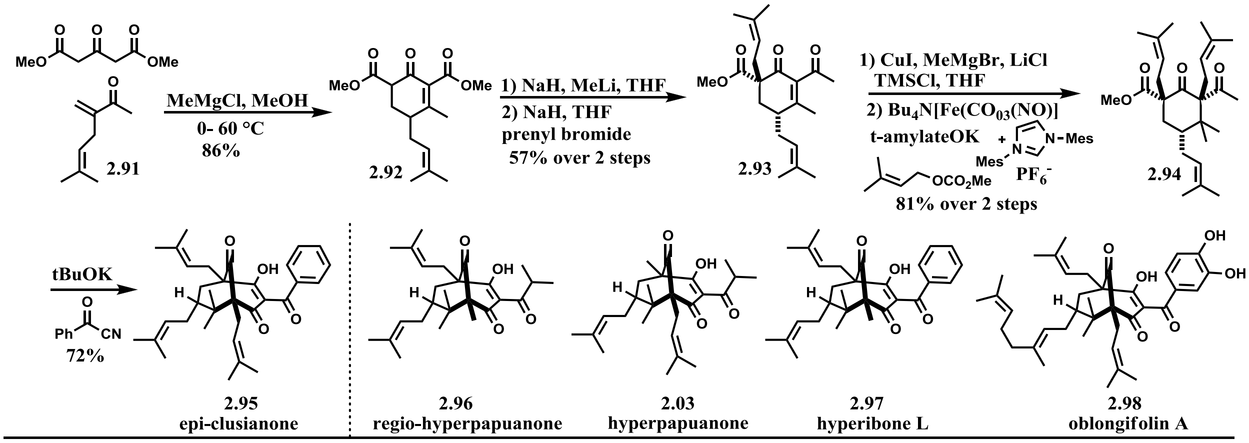


Scheme 2.13 *Intramolecular aldol reaction for the total synthesis of ent-hyperforin (**2.07**) by Shibasaki*

Sixteen more steps were necessary to install the allyl and prenyl side chains and to form the bicyclic core (**2.87**) via an aldol reaction. From this advanced intermediate (**2.88**), they concluded the first synthesis of *ent*-hyperforin (**2.07**) in twenty-one additional steps.

Although it may seem as a synthetic tour de force, the presence of numerous protecting groups and tedious oxidation state manipulations plagues the practicality of this synthesis.

The last synthesis, based on the bridgehead annelation of a polyfunctionalized cyclohexanone derivative, possessed a significantly reduced number of steps to achieve its target. While the synthesis developed by Plietker seems limited to alkyl groups on the bridgehead substituents, it is a short and high-yielding synthetic approach which is quite generally applicable towards *trans*-type B PPAPs (**Scheme 2.14**).[25] The key step consists of a Dieckman condensation of a congested cyclohexanone (**2.94**) to construct fully substituted bridgehead scaffolds bearing the correct oxidation state. The Dieckman precursor (**2.94**) was assembled via a tandem Michael addition/Knoevenagel condensation. This modular synthetic approach enabled the total synthesis of three natural products (**2.03**), (**2.97**) and (**2.98**) and two non-natural products (**2.95**) and (**2.96**).

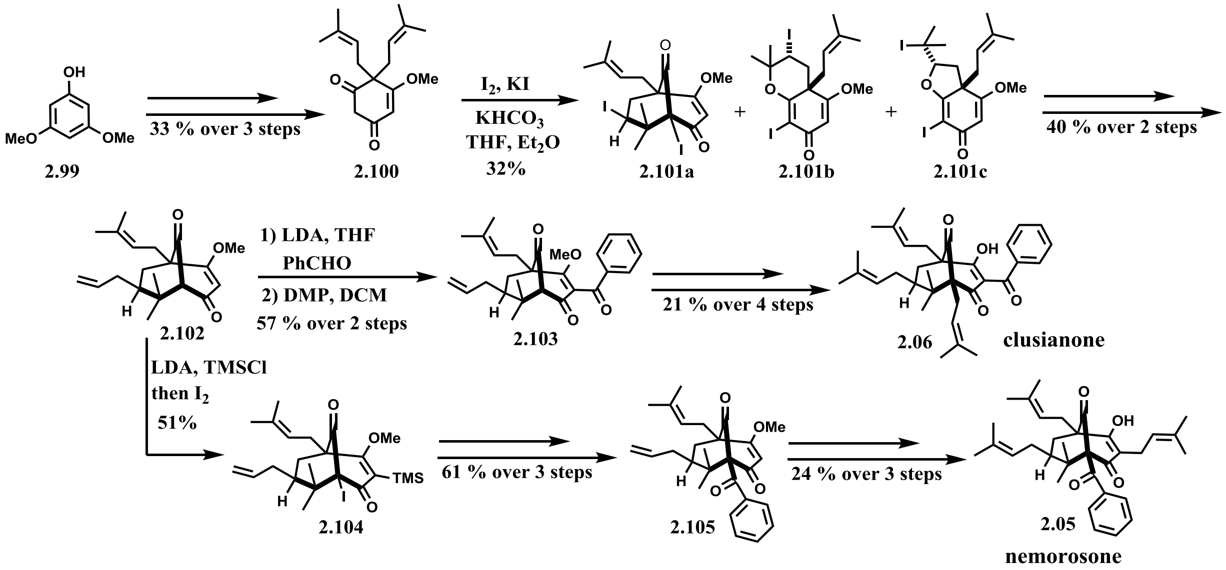


Scheme 2.14 *Dieckmann condensation for the total synthesis of five different PPAPs by Plitker*

2.6 Total synthesis of PPAPs: second synthetic strategy

The second general synthetic strategy is the alkylative dearomatization of substituted phenols, a biomimetic synthetic approach which has allowed the shortest synthesis of clusianone (**2.06**) to date, completed by Professor Porco.[27a] This strategy was initiated by Professor Danishefsky, another prolific contributor to this area, with the synthesis of garsubellin A **(2.08)**, clusianone (**2.06**) and nemorosone (**2.05**). [26] While Danishesfky used the same synthetic strategy for all three targets, only the syntheses of clusianone (**2.06**) and nemorosone (**2.05**), which used differentiation of non-conventional carbanions, will be presented (**Scheme 2.15**). [26a,b] The divergent synthesis starts with 3,5-dimethoxyphenol (**2.99**), which undergoes a double palladium(0)-catalyzed allylation followed by a cross methathesis reaction with 2-methylbut-2-

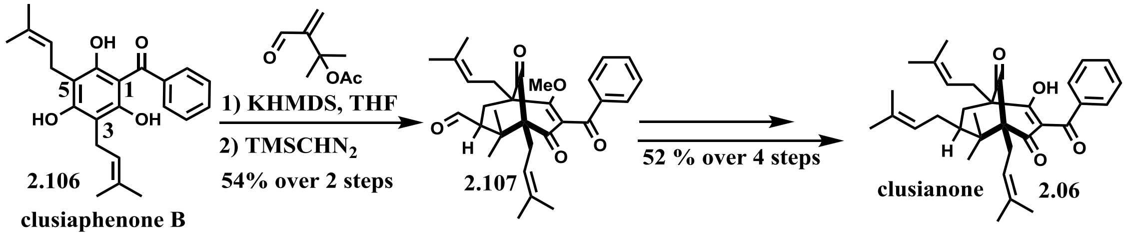
ene. A further monodemethylation afford dearomatized *gem*-diprenyllated product (**2.100**) in 33% yield over three steps. The common intermediate (**2.102**) that served as the branching point for the two naturally occurring PPAPs was constructed by an iodine-induced cyclization method developed by this research group during the synthesis of garsubellin A (**2.08**). Due to the lack of the furano-fused ring that provides further rigidity to the molecule, this transformation was less selective on monocyclic compound (**2.100**) and led to the desired bicycle in a moderate 32% isolated yield. It is important to note that, a more selective transformation was carried out during the synthesis of garsubellin A (**2.08**).[26c] Finally, the Danishefsky group was able to generate, exploit and differentiate non-conventional carbanions and finish both syntheses from a common intermediate (**2.102**). Six more steps were needed to correctly add the acetophenone and the prenyl side chains in order to access clusianone **(2.06)** and seven more steps were needed to add these two substituents in an inverse order and access nemorosone **(2.05)**.



Scheme 2.15 *Differention of non-conventional carbanions for the divergent synthesis of clusianone (**2.06**) and nemorsone (**2.05**) by Danishefsky*

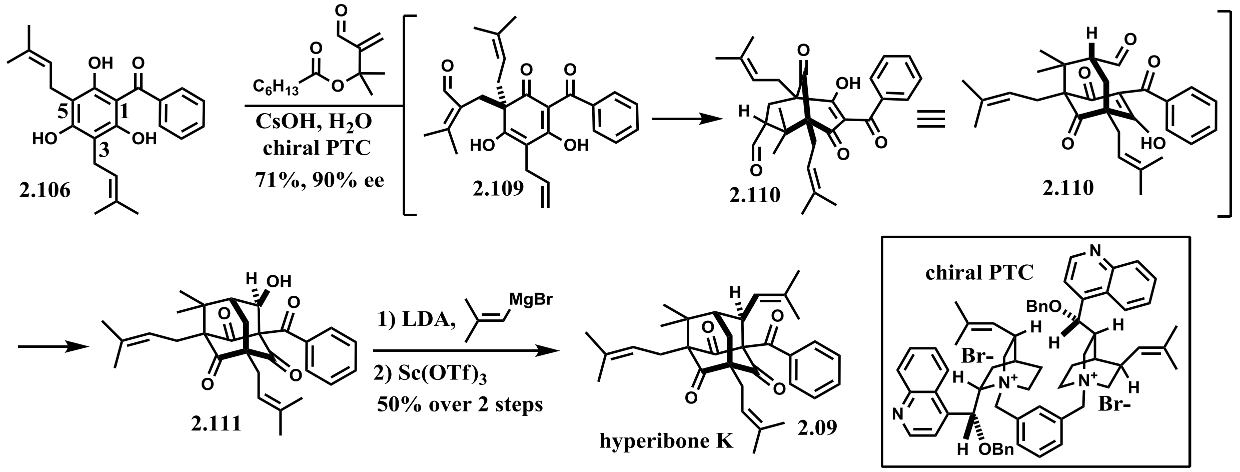
Inspired by biosynthetic considerations, Porco conceived an ingenious and highly expedient synthetic approach to the synthesis of PPAPs.[27] In this approach, an alkylation dearomatization/annulation strategy was developed to directly access the bicyclic core structure of the PPAPs from clusiaphenone B (**2.106**). The reaction between a *bis*-Michael acceptor and clusiaphenone B **(2.106)** led to an annulated product, which was readily methylated with $TMSCHN_2$ and isolated in 54% yield over two steps.

Conversion of the aldehyde in the compound (**2.107**) into the remaining prenyl side chain was executed through a four steps sequence and finalized the synthesis of clusianone (**2.06**).



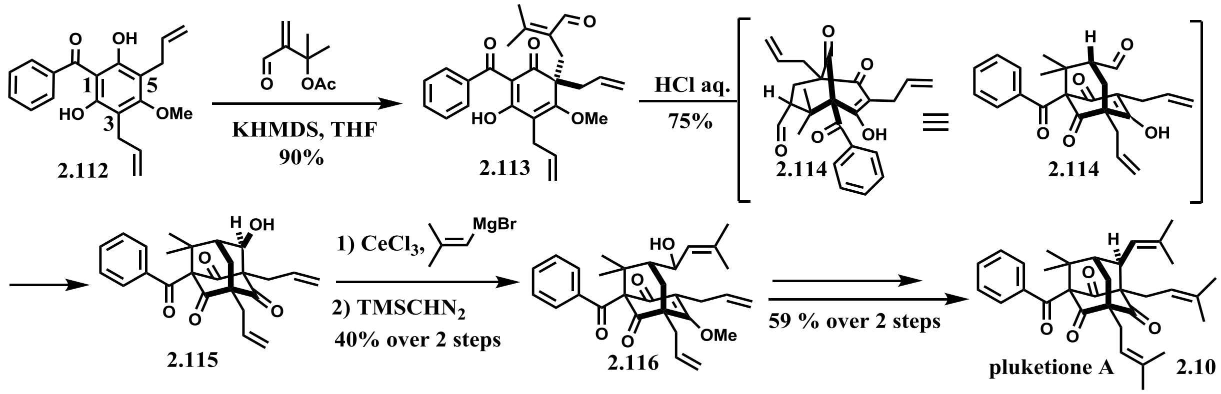
Scheme 2.16 *Alkylative dearomatization/annulation reaction for the synthesis of clusianone (**2.06**) by Porco*

Three years later, using the same synthetic approach, Porco and co-workers achieved an enantioselective synthesis of the adamantane-containing PPAP natural product, hyperibone K (**2.09**) (**Scheme 2.17**).[27b] An asymmetric dearomatization/alkylation sequence was investigated under phase-transfer conditions in the presence of a cinchona alkaloid as the chirality inducer. Dimeric cinchona alkaloid (chiral PTC) was identified as the most effective catalyst, which, in combination with heptanoate aldehyde, furnished adamantane (**2.111**) in 71% yield and 90% *e.e.* This asymmetric transformation leads to bicyclic intermediate (**2.110**), which is the epimer of bicyclic (**2.107**). This epimeric aldehyde (**2.110**) is well oriented to undergo another carbon-carbon bond formation and generated the adamantane ring (**2.11**). Two additional steps were required to install the last vinyl moiety and finish the synthesis of hyperibone K **(2.09).**



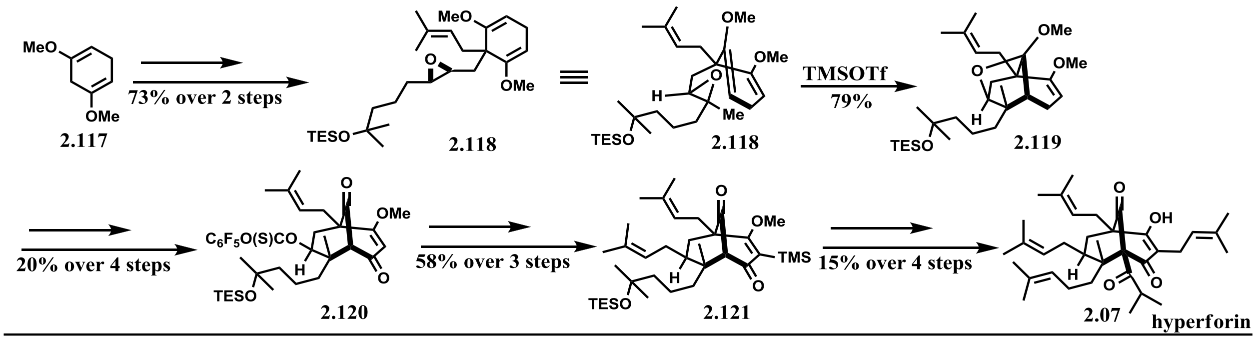
Scheme 2.17 *Alkylative dearomatization/annulation reaction for the enantioselective synthesis of hyperibone K (**2.09**) by Porco*

In order to access the isomeric adamantane natural product pluketione A **(2.10**), Porco had developed a site-selective dearomatization/annulation of a clusiaphenone B derivative (**2.112**).[27c] A methyl ether protected clusiaphenone B (**2.112**) was employed with the intention that the alkylation dearomatization sequence would take place at the C5 and C1 rather than at the C5 and C3. It was found that the masked hydroxyl group at C5 disfavors carbon-carbon bond formation at C3. Thus, treatment of compound (**2.112**) with LiHMDS in the presence of a bis-Michael acceptor afforded the monoalkylated dearomatized product (**2.113**) in 90% yield. Exposure of intermediate (**2.113**) to concentrated HCl eventually led to the production of adamantane (**2.115**) in 75% yield as a single diastereoisomer. The synthesis of pluketione A (**2.10)** was completed almost in the same way as hyperibone K (**2.09)** with the addition of the last vinyl side chain.



Scheme 2.18 *Alkylative dearomatization/annulation reaction for the synthesis of pluketione A (2.10) by Porco*

Recently, Shair reported a short and elegant enantioselective synthesis of hyperforin (**2.07**) (**Scheme 2.19**).[28] This last synthetic approach could be seen as a combination of the two general synthetic strategies. While they did not perform the dearomatization of a symmetric aromatic intermediate, they exploited the latent symmetry of intermediate (**2.118**) which also allowed them to incorporate some elements of modularity during the synthesis. After two alkylations of cyclohexadiene (**2.117**), the bicyclic bridgehead scaffold (**2.101**) was obtained via the Lewis acid mediated opening of epoxide (**2.118**). After oxidation and functional groups manipulation, intermediate (**2.120)** is set up for an allyl radical addition. Protection of the vinyligous ester moiety afforded intermediate (**2.121**) which is only missing the acyl bridgehead group. Contrary to Danishefsky's and Simpkins' synthesis, functionalization of the bridgehead carbon was accomplished in a one-pot reaction and subsequent deprotection delivered hyperforin (**2.07**) over 14 steps from cyclohexadiene (**2.117**). Due to the adjacent quaternary center, functionalization of this last bridgehead carbon remains the biggest challenge in the synthesis of PPAPs.

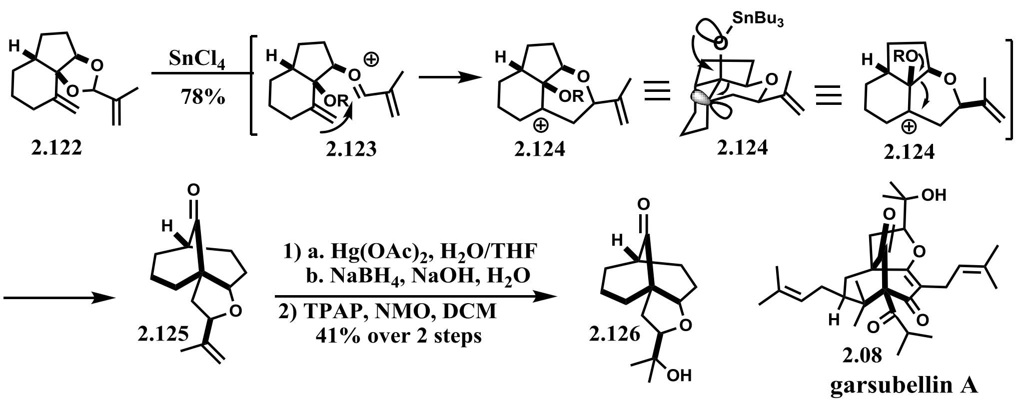


Scheme 2.19 *Enantioselective total synthesis of hyperforin (**2.07**) by Shair*

2.7 Previous work towards the synthesis of PPAPs in the Barriault lab

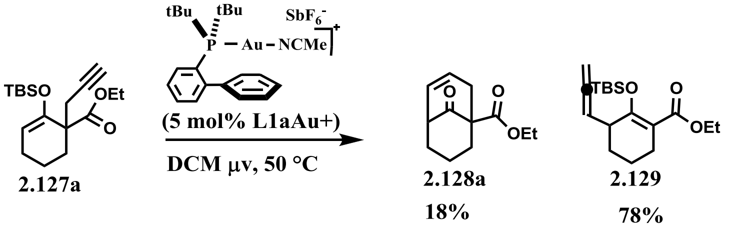
Numerous synthetic efforts have been made to achieve the synthesis of PPAPs, resulting in innovative synthetic strategies to access the bridged bicyclic core and in new methodologies for sterically hindered C-C bond forming reactions. Comparing the structural similarities between the PPAPs, one could deduce that the wide range of biological properties of these compounds arise from small variations. Their common bicyclic framework can be viewed as a tridimensional structure that helps to arrange the corresponding tethers in the accurate orientation. As this remarkable structure-activity relationship is still misunderstood, the development of a general and efficient synthetic strategy to prepare most members of the family and elaborate a natural-unnatural library of compounds is of paramount importance.

Prior to the work on gold(I)-catalysis, our group tackled the synthesis of a member of the PPAP family, garsubullin A (**2.08**), using a Prins-Pinacol approach (**Scheme 2.20**). A former group member, Mélina Girardin, synthesized the tricycle bridged core of garsubellin A **(2.08)** via an ingenious Prins-Pinacol cascade.[29] The acetal (**2.122**) was exposed to tin(IV) chloride to afford the bicyclo[3.3.1]nonane (**2.125**) in 78% yield. After acetal opening, the resulting oxocarbenium (**2.123**) undergoes a Prins cyclization leading to the tertiary carbocation (**2.124**). The latter rearranges to compound (**2.125**) via a semi-pinacolic rearrangement. This domino process quickly delivers the tricyclic core of garsubellin A (**2.08**). This strategy is particularly adapted for garsubellin A (**2.08**), but was not of general applicability to generate the bicyclic scaffold for the whole PPAPs family.



Scheme 2.20 *Prins-Pinacol strategy towards the tricyclic bridge core of garsubellin A*

The discovery of a novel gold(I)-catalyzed benzannulation by Christiane Grisé-Bard (Ph. D. student), which generates functionalized tetrahydronaphthalenes, developed in our group an interest for the field of gold catalysis.[30] Rapidly, the Barriault group hypothesized that gold(I) catalysis could be very useful in producing sterically hindered bridged bicylic scaffolds (**Scheme 2.21**). Taking advantage of the affinity of phosphino gold(I) salts for triple bonds, we envisioned a gold(I)-catalyzed 6-*endo-dig* carbocyclization of cyclic silyl enol ethers to synthesize bicyclic bridgehead ketones. Initial work done by Geneviève Bétournay (honors student), revealed that the gold(I)-catalyzed carbocyclization of silyl enol ether (**2.127a**) gave the desired product (**2.128a**) in 18% yield under microwave condition. Interestingly, allene (**2.129**) was isolated in 78% yield . The major product of the reaction, compound (**2.129**), was the result of a formal sigmatropic shift of the alkyne.

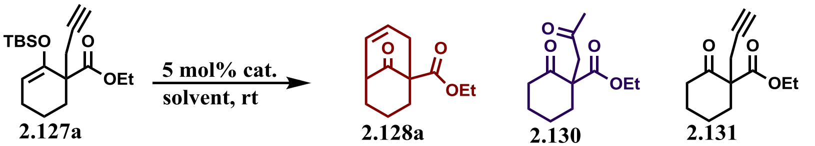


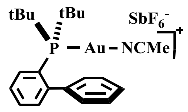
Scheme 2.21 *Preliminary result in the synthesis of bridged carbocycles via a gold(I)-catalyzed 6-endo-dig carbocylization*

2.8 Catalyst and reaction condition optimization

With this result in our hands, we next examined various catalyst, solvent and reaction conditions. The results are shown in **Table 2.01**.[31] Treatment of silyl enol ether (**2.127a**) with 5 mol % of triphenylphosphinegold(I) chloride and 10% of water in DCM at room temperature gave the bridged ketone (**2.128a**) in low conversion (30%) (**entry 1**). The major by-product was the ketone (**2.131**) resulting from the hydrolysis of silyl enol ether (**2.127a**).

The side product (**2.130**) was also isolated in significant quantity. The latter is the result of a competing triple bond hydration. The replacement of triphenylphosphine by triethylphosphine dramatically improved the chemoselectivity (30:1) and the conversion (76%) (**entry 2**). Moreover, the choice of ligand, solvent and counterions seemed to be play a key role in the reaction selectivity (**entries 3-8**). After considerable experimentation, we found that the use of (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate **(L1aAu+)** (5 mol%) in acetone afford the desired product (**2.128a**) in 90% isolated yield (**entry 8**).[32]

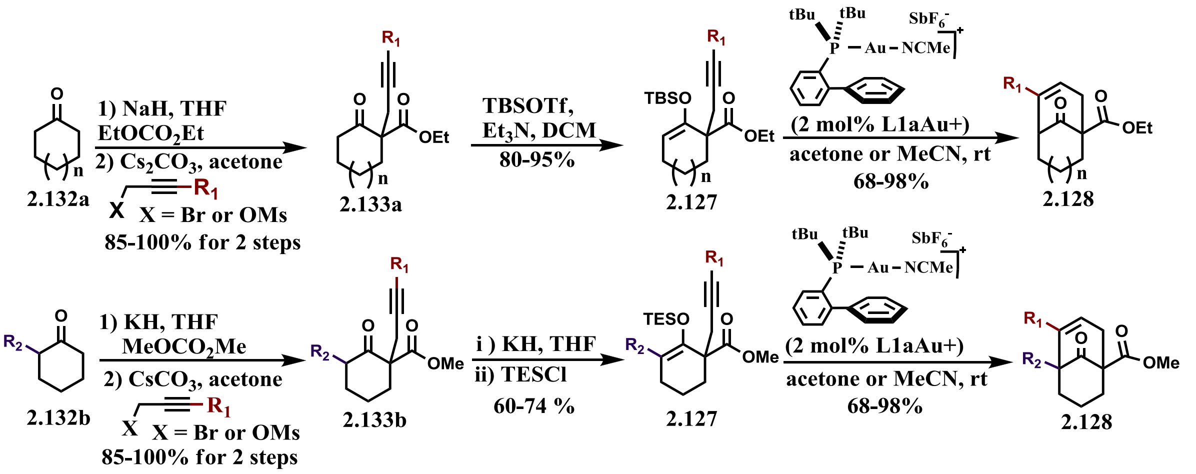


Entry	Catalyst	Solvent	Temps	Conversion[1]	Mixture[1] 2.128 : 2.130
1	$Ph_3P\text{-}AuCl$ / $AgBF_4$	DCM / H_2O	7h	30 %	8.0 : 1.0
2	$Et_3P\text{-}AuCl$ / $AgBF_4$	DCM	7h	76 %	30 : 1.0
3	$Et_3P\text{-}AuCl$ /$AgSbF_6$	DCM	6h	78 %	14 : 1. 0
4	$Et_3P\text{-}AuCl$ / AgOTf	DCM	6h	100%	2.5 : 1.0
5	 L1aAu+	DCE	4h	100%	1.0 : 5.0
6		Toluene	4h	88 %	37 : 1.0
7		ACN	4h	100 %	4.5 : 1.0
8		Acetone	3h	100 %	30 : 1.0

1: Conversion and mixture determined by ^1H-NMR

Table 2.01 *Optimization of the 6-endo-dig carbocylization toward the synthesis of bridged carbocycles*

Surprisingly, the air stable JohnPhosGold(I) complex (**L1aAu+**), developed by Echavarren and co-workers, gave mainly the hydration product (**2.130**) in dichloroethane (**entry 5**). It is important to outline that the question of the reproducibility of this transformation could be an interesting issue. Indeed at the time that this research was done, we were not aware of the important aspect of the water and we did not try to use dry or wet dichloromethane to observe the impact on the chemoselectivity (**entry 5**). However, this aspect will become important for more challenging gold(I) catalyzed reactions (see chapters 4 and 5). Various solvents are suitable for this transformation, but additional experiments demonstrated that acetone was the optimal solvent for this process and 2 mol% of catalyst can be used without diminishing the conversion. With efficient and mild reaction conditions in hand, we examined the scope and limitations of the reaction.

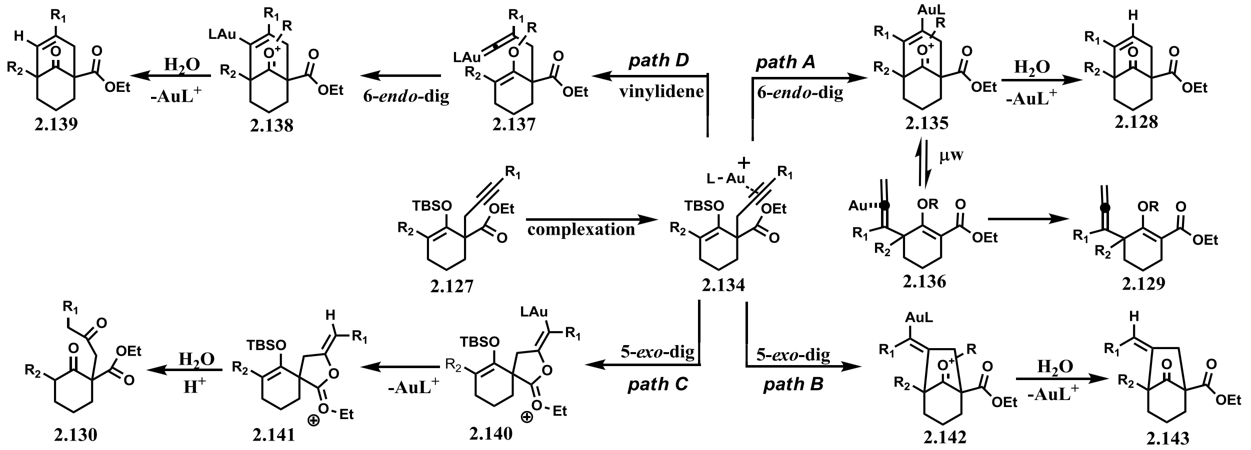


Scheme 2.22 *Two synthetic sequences, R1 and R2 substitutions on the bridged carbocycles*

The preparation of the bridged carbocyles is presented in **Scheme 2.22**. The synthesis of silyl enol ether (**2.127**) began with commercially available cycloalkanone (**2.132a**), which underwent an acylation with sodium hydride and diethylcarbonate in refluxing THF. The installation of the propargyl unit was accomplished using very mild reaction conditions, cesium carbonate in acetone at room temperature. The conversion of ketone (**2.133a**) to the corresponding silyl enol ether (**2.127**) was performed using *tert*-butyldimethylsilyl triflate and triethylamine in dichloromethane. In order to synthesize the substrate with the corresponding **R2** tethered, we started the synthesis with readily available α-substituted cyclohexanone (**2.139**). The ketone (**2.133b**) was also prepared via an acylation reaction and nucleophilic addition to propargyl bromide. An excess of potassium hydride in refluxing THF with dimethylcarbonate already present was necessary to effectively trap the kinectic enolate before thermodynamic equilibrium. The formation of silyl enol ether (**2.127**) proved to be more difficult to perform. It was necessary to use potassium hydride in refluxing THF for the deprotonation followed by the addition of triethylsilyl chloride to obtain the desired enol ether (**2.127**). Having established a concise route to prepare the silyl enol ethers (**2.127**) embedded with **R1** and **R2** substituents, the mechanism and scope of the 6-*endo-dig* carbocyclization was then investigated.

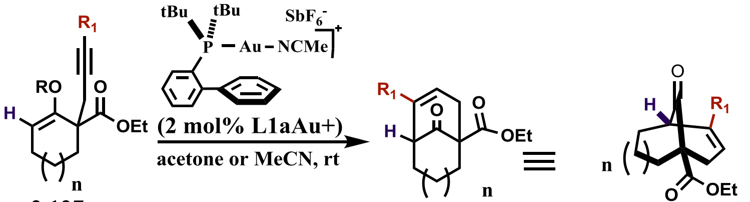
2.9 Scope and mechanism of the gold(I)-catalyzed 6-endo-dig carbocyclization for the synthesis of bridged carbocycles

A cursory inspection of the mechanism reveals that the Au(I)-carbocyclization can operate via four distinct pathways. In path A, a 6-*endo-dig* carbocyclization generates intermediate (**2.135**) which upon protodeauration and hydrolysis gives the desired compound (**2.128**). Conversely, a competititve 5-*exo dig* cyclization can lead to compounds (**2.130**) and (**2.143**) via vinyl gold(I) intermediates (**2.140**) and (**2.142**) respectively (path B and C). It was suggested that the formation of the secondary product (**2.130**) comes from an intramolecular addition of the ester instead of an intermolecular addition of water on the alkyne. Finally, the interaction of the triple bond and the gold(I) catalyst can result into the formation of a vinylidene complex (**2.137**), which undergoes a 6-*endo-dig* carbocyclization to give the bicyclo[3.3.1]nonanone (**2.139**) where the alkyne substituent has migrated to the internal carbon. Deuteration of vinyl gold(I) species can determine effectively which mechanism between path A and D is in operation during our gold(I)-catalyzed carbocyclization. Even the cyclization tolerates alkyl and aryl functionalities for the **R2** substituent without migration, we did not rule out the possibility of the reaction occurring via pathway D. As we will see later, this pathway can be accessible when a good migratory group is present on the triple bond, such as an iodide.



Scheme 2.23 *Proposed mechanistic pathways for the gold(I)-catalyzed carbocyclization*

Although several methods have been developed to construct carbon bridged carbocyles of-medium sized rings, most of them are specific to a particular scaffold. Consequently, the first variation in the scope that we performed was the size of the ring template (**Table 2.02**). With silyl enol ether (**2.127b**), (**2.127c**) and (**2.127d**), we demonstrated that bicyclo[2.3.1]octanone (**2.128b**), bicyclo[4.3.1]decanone (**2.128c**), and bicyclo[5.3.1]undecanone (**2.128d**) could be accessed efficiently via the gold(I)-catalyzed carbocyclization with 85%, 82% and 98% respectively (**entries 1, 2** and **3**). These results demonstrated unequivocally that bridged bicyclic frameworks of various sizes could be generated efficiently by this method. Interestingly, cyclization on ring sizes of odd number (5 & 7) required acetonitrile as solvent instead of acetone in order to obtain better chemoselectivity. As previous work in the field of gold(I)-catalysis focused primarily on terminal alkynes, we next examined the substitution of the triple bond. To our delight, methyl and phenyl substituents were well tolerated and yielded to the bicyclic ketone (**2.128e**) and (**2.127f**) in 92% and 88% respectively.



2.127 2.128 2.128

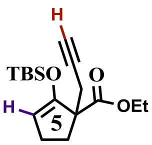
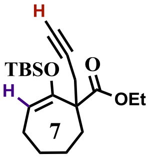
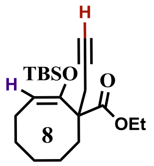
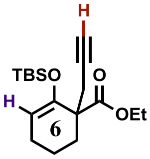
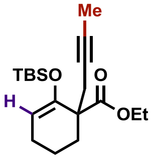
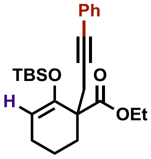
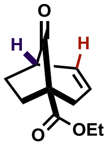
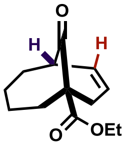
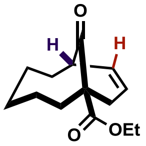
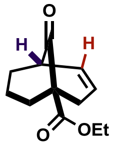
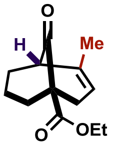
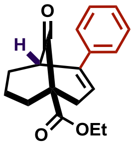
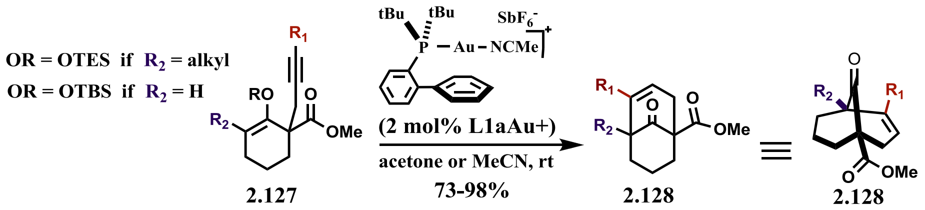
Entry	1	2	3	4	5	6
Substrate	 2.127b	 2.127c	 2.127d	 2.127a	 2.127e	 2.127f
Solvent Time	acetonitrile 12h	acetonitrile 25h	acetone 1h	acetone 3h	acetone 6h	acetone 7h
Product	 2.128b	 2.128c	 2.128d	 2.128a	 2.128e	 2.128f
Yield%	85%	82%	98%	90%	92%	88%

Table 2.02 *Scope of the 6-endo-dig carbocyclization: R1 substitution*

In the context of its application to the total synthesis of natural polycyclic polyprenylated acetylphloroglucins (PPAPs), we further probed the scope of this transformation with substrates possessing tetrasubstituted enol ether to afford bicycles with two bridgehead quaternary centers (**Table 2.03**). With this goal in mind, we used methyl and allyl substituents, as is found in natural PPAP, and isolated the corresponding bicyclo[3.3.1]nonanone (**2.128g**) and (**2.128h**) in 91% and 87% yields respectively. In order to increase the steric environment during the catalytic process and push the limits of our carbocyclization, we prepared various substrates possessing both substituents at **R1** and **R2** positions.

Gratifyingly, the cyclization worked as well as anticipated (**entries 3** and **4**). Even the addition of a strong electron withdrawing group at the *para* position of the aromatic ring did not affect the regioselectivity (**entry 6**). The results displayed in **Table 2.03** show the attractive aspect of this method, which relies on the ability to easily construct bicyclo[m.n.1]alkanones, bearing two bridgehead quaternary carbon centers, under mild reaction condition.



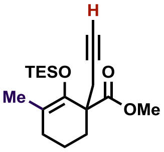
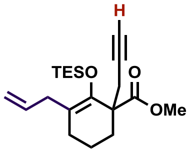
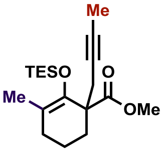
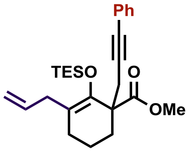
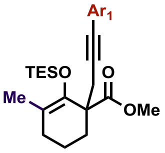
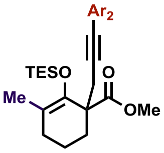
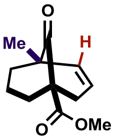
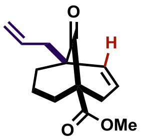
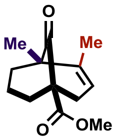
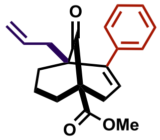
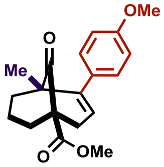
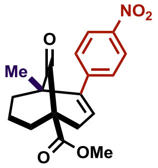
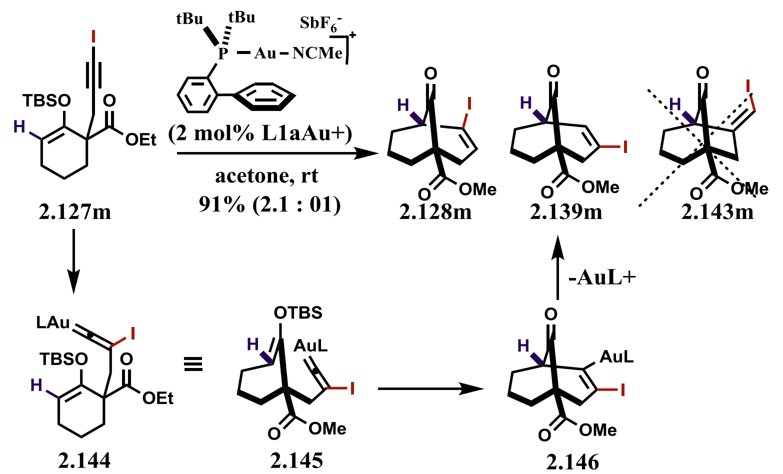
Entry	1	2	3	4	5	6
Substrate	 **2.127g**	 **2.127h**	 **2.127i**	 **2.127j**	 **2.127k**	 **2.127l**
Solvent	acetone	acetone	acetonitrile	acetone	acetone	acetone
Time	6 h	6 h	40 h	15 h	15 h	25 h
Product	 **2.128g**	 **2.128h**	 **2.128i**	 **2.128j**	 **2.128k**	 **2.128l**
Yield%	91%	87%	94%	92%	88%	83%

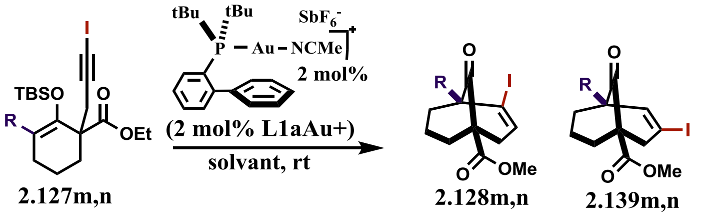
Table 2.03 *Scope of the 6-endo-dig carbocyclization: R1 and R2 substituted bicyclic ketone*

The cyclization using propargylic iodide and bromide such as (**2.127m**) and (**2.127o**) was then investigated (**Scheme 2.24** and **2.25**). Treatment of the iodide derivative (**2.127m**) under standard conditions produced the desired ketone (**2.128m**), along with an isomeric product in ratio of 2.1:1 (91% yield). In our original communication, we identified the side product as being ketone (**2.143m**). However, further experimental evidences confirmed that this compound was misassigned and the correct structure is that of compound (**2.139m**).[33] It formation could be explained by the generation of the vinylidene intermediate (**2.144**) and migration of the iodide to the internal carbon. After carbon-carbon bond formation and protodeauration, the bicyclic (**2.139m**) can be isolated. Therefore, the competitive path B, resulting from a 5-*exo-dig* cyclization, was never observed for these bridged bicyclic scaffolds.



Scheme 2.24 *Gold(I)-catalyzed 6-endo-dig carbocyclization of iodoalkyne*

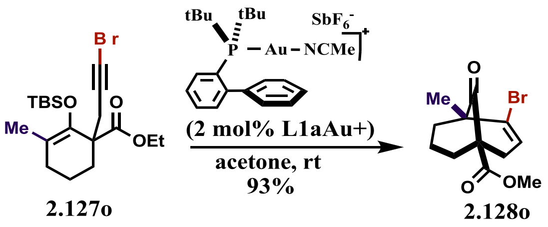
The effect of the solvent on these competing pathways was then investigated. The replacement of acetone by benzene as solvent gave similar results, while the occurrence of the π-acid pathway is slightly enhanced (**entry 2**). Surprisingly, the use of chloroform gave great selectivity for the desired vinyl iodide (**2.128m**), while in MeOH the vinylidene pathway was preferentially followed, favoring the formation of vinyl iodide (**2.139m**) (**entries 3** and **4**).



Entry	R	Substrate	Solvant	Yield	Mixture 2.128 : 2.139
1	H	2.127m	acetone	91%	2.1 : 1.0
2	H	2.127m	benzene	88%	2.9 : 1.0
3	H	2.127m	$CHCl_3$	85%	12.5 : 1.0
4	H	2.127m	MeOH	68 %	1.0 : 1.2
5	Me	2.127n	acetone	88%	1.2 : 1.0
6	Me	2.127n	benzene	83%	2.6 : 1.0
7	Me	2.127n	$CHCl_3$	92%	10.3 : 1.0
8	Me	2.127n	MeOH	73 %	1.0 : 2.3

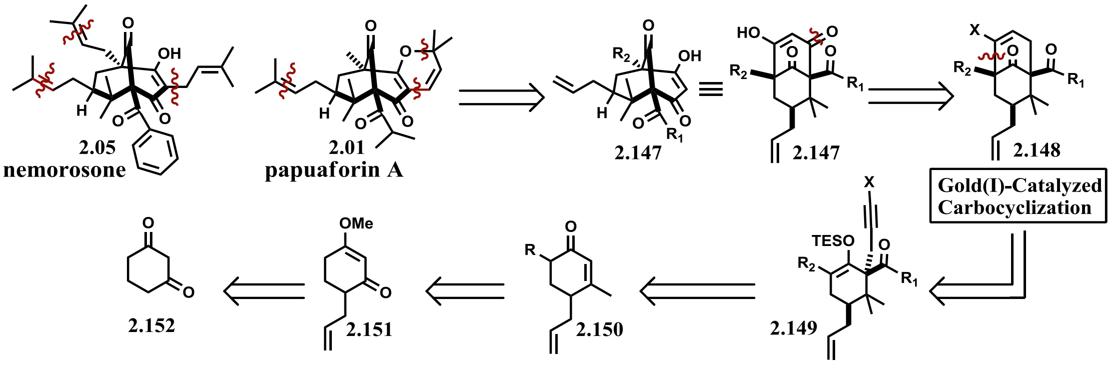
Table 2.04 *Gold(I)-catalyzed 6-endo-dig carbocyclization of iodoalkynes*

The formation of a quaternary center during the cyclization had no effect on whether the solvent favored a competitive pathway (**entries 5-8)**, but the enhancement of steric hindrance seemed to slow down the cyclization of the classic π-acid intermediate**.** To our delight, the Au(I)-catalyzed cyclization of the bromoalkyne (**2.127o**) gave the vinyl bromide (**2.128o**) with both bridgehead substituents in 93% yield as the sole isomer (**Scheme 2.25**). This last satisfactory result concluded our preliminary investigation on model compounds.



Scheme 2.25 *Gold(I)-catalyzed 6-endo-dig carbocyclization of bromoalkyne*

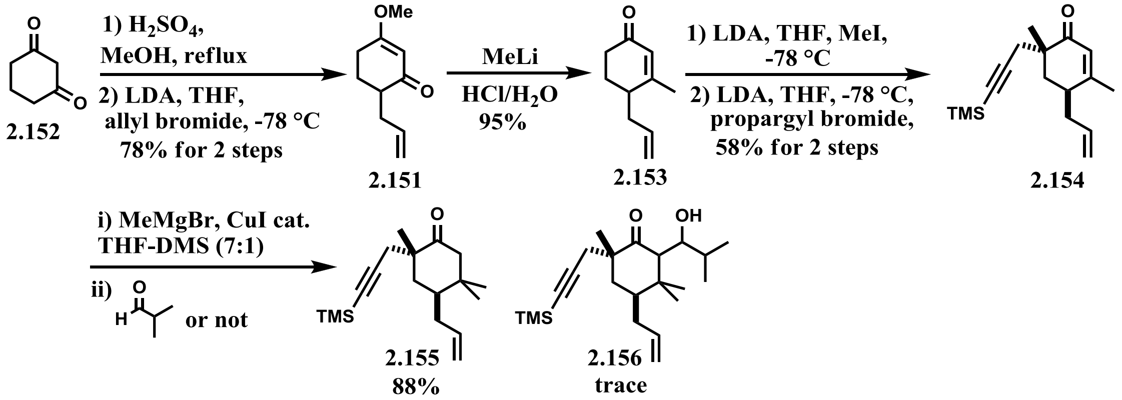
Owing to the mild and efficient reaction condition, we were thrilled to apply the Au(I)-catalyzed cyclization toward the total synthesis of complex PPAPs (**Scheme 2.26**). One can recognize that an intermediate such as (**2.147**) could act as a common bridehead ketone for the modular synthesis of various PPAPs such as papuaforin A (**2.01**) and nemorosone (**2.05**). This β-ketoenol (**2.147**) could come from an allylic oxidation of a well substituted cycloalkene (**2.148**). This latter compound could be obtained via our gold(I)-catalyzed 6-*endo-dig* carbocyclization between an alkyne and a silyl enol ether. The compound (**2.149**) could be derived from a 1-4 methyl cuprate addition and enolate trapping with a defined aldehyde. Finally, the synthesis of enone (**2.150**) would follow a synthetic sequence developed by Storke and Danheiser for the synthesis of multi-functional cyclohexenone.



Scheme 2.26 *Our gold(I)-catalyzed retrosynthetic analysis of the PPAP family*

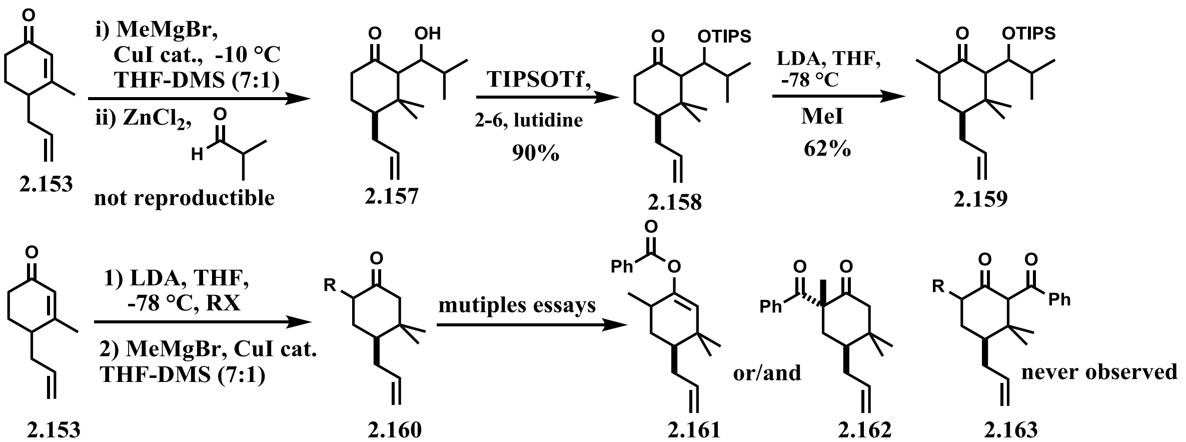
2.10 Synthesis of an advanced intermediate towards synthesis of PPAPs

We started our synthesis with a sequence developed by Storke and Danheiser for the synthesis of poly-functionalized cyclohexenone (**Scheme 2.27**).[24] Treatment of commercially available diketone (**2.152**) with sulfuric acid in refluxing methanol gives the corresponding vinylogous ester, which is subsequently allylated by deprotonation with LDA and treatment of the resulting enolate with allyl bromide. The addition of methyllithium to the vinylogous ester (**2.151**) led to a [1,3]-ketone transposition. Two subsequent alkylations installed the first quaternary center in 58% yield over two steps.



Scheme 2.27 *First synthetic route, failure of the one-pot conjugate cuprate addition and aldolisation*

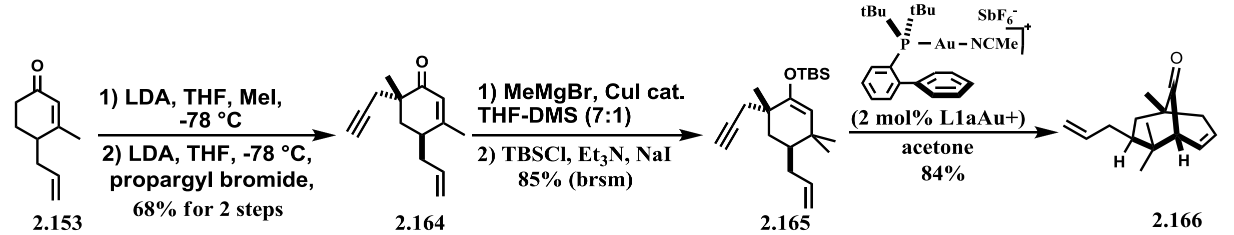
While we were not able to repeat the work of Shibasaki on sterically crowded enone (**2.154**), we tried the one-pot cuprate addition and enolate trapping on a less functionalized intermediate (**2.153**).[18c] Shibaski reported the transformation of enone (**2.153**) to ketone (**2.157**) on a forty gram scale with a more than acceptable yield of 76%. We repeated this protocol and we even modified it to facilitate the formation of the second carbon-carbon bond, but we were not able to efficiently replicate this manipulation and produce enough material to continue the synthesis further. We succeeded, to the best of our capacity, to protect the alcohol (**2.157**) with TIPSOTf and perform a mono-alkylation on ketone (**2.158**) to access ketone (**2.159**).



Scheme 2.28 *Unsuccessful functionalization of the carbon adjacent to the quaternary center*

The problem was the formation of the second carbon-carbon bond and not the addition of the cuprate to the enone. Thus, we decided to explore other avenues such as a kinetically-controlled acylation of α-monosubstituted ketone (**2.160**) (**Scheme 2.28**). With the collaboration of co-op student Gabriel Bellavance, we screened numerous conditions and unfortunately never observed acylation at the desired carbon (**2.163**). Even upon changing the nature of the base, the kind of the electrophile or the solvent, we only observed competition between O-acylation (**2.161**) and C-acylation on the thermodynamic side of the ketone (**2.162**). The thermodynamic and kinetic reactivity of ketones can normally be controlled on α-monosubstituted cycloalkenones; however the quaternary center beta to the carbonyl perturbs this simple analysis. In our case, insertion of the *gem*-dimethyl on the cyclohexanone template prevents the carbon-carbon bond formation, which would generate the desired substituted cyclohexanone (**2.163**).

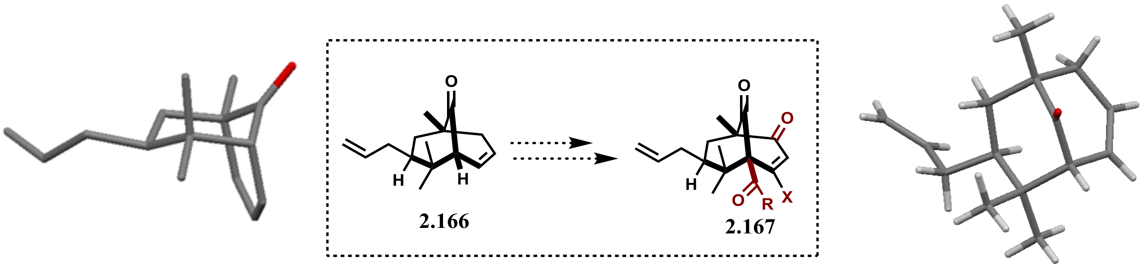
Finally after much deliberation, we decided to defer the installation of this substituent until after the cyclization and perform directly a dialkyaltion on enone (**2.153**). The first alkylation occurred with LDA and MeI and the second with LDA and propargyl bromide, furnishing the enone (**2.164**) in 68% yield over two steps and in a diastereoisomeric ratio of 3: 1 in favor of the desired one. A conjugate cuprate addition followed by the formation of the silyl enol ether gave monocyclic intermediate (**2.165**) in good yield. Our gold(I) catalyzed 6-*endo-dig* carbocyclization provided the advanced bridged bicyclic intermediate (**2.166**) in 84% yield.



Scheme 2.29 *Successful sequence towards the synthesis of an advanced bicyclic intermediate*

With this developed synthetic sequence, we have stereoselectively accessed the bicyclic advanced intermediate (**2.166**) in eight steps and 33% overall yield. This accomplishment proves the utility of the gold(I)-catalyzed 6-*endo-dig* carbocyclization towards the total synthesis of PPAP natural products. However, two major challenges remain to overcome for the synthesis of PPAPs: 1) the functionalization of bridgehead carbons adjacent to the quaternary center and 2) the selective oxidation of the cyclic alkene.

At this time, the second challenge was briefly investigated but without any significant findings, just the anticipated difficulties. As the application of our methodology to the synthesis of fused carbocycles was more than interesting, my research was guided towards a better understanding of gold(I) catalysis and my synthetic endeavor towards papuaforin A (**2.01**) ends with the advanced intermediate (**2.166**). However, Gabriel Bellavance succeeded with a similar approach to synthesize more than four members of the PPAP family.



Scheme 2.30 *X-ray of bridged bicyclic ketone (**2.166**) and unaddressed challenges*

2.11 Summary of the gold(I)-catalyzed synthesis of bridged carbocycles

In summary, we have developed a mild and efficient method to generate bicyclo[m.3.1]alkenones using JohnPhos gold(I) complex (**L1aAu+)** as catalyst. The attractive features of this method reside in its ability to construct carbon bridged-medium rings of various sizes and to install two quaternary carbon centers adjacent to the bridgehead ketone. This methodology has enabled us to synthesize an advanced intermediate in our efforts towards the natural product papuaforin A **(2.01)**.

2.11 References

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Chapter 3

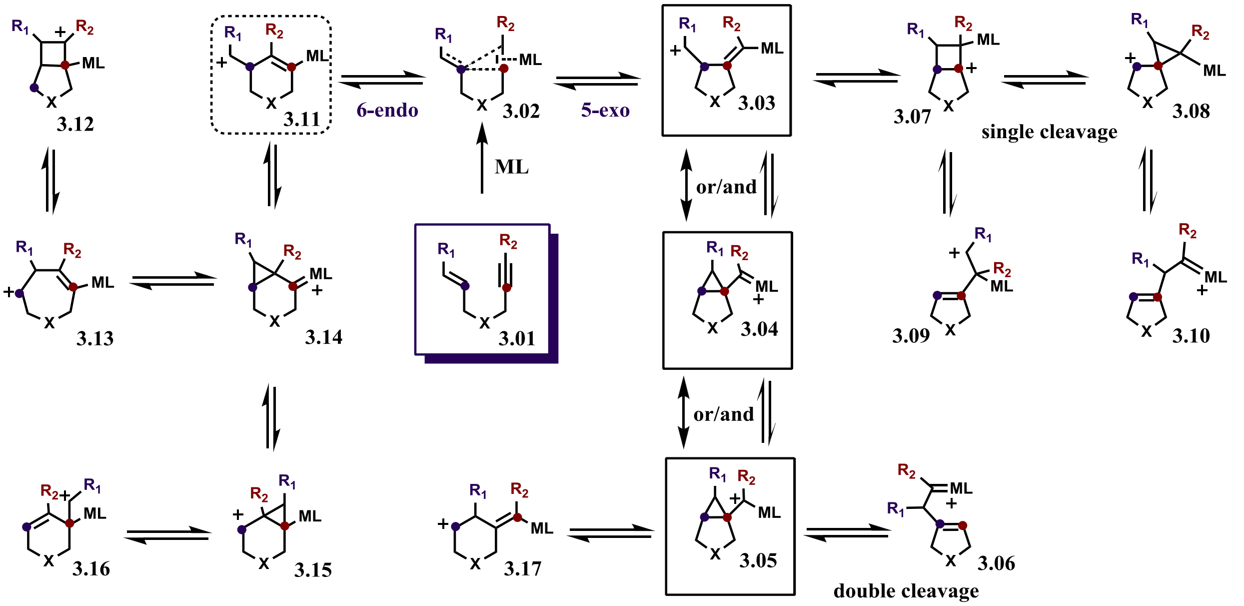
Selective Divergent Synthesis of Fused Carbocycles via a Gold(I)-Catalyzed Carbocyclization

3.1 Introduction to the cycloisomerization of 1,6-enynes

By virtue of their unique ability to chemoselectively activate carbon–carbon triple bonds as soft Lewis acids combined with its ability to stabilize cationic intermediates, gold(I) complexes are highly efficient catalysts for the discovery of novel selective transformations.[1] Gold(I)-catalyzed reactions offer milder reaction conditions and better selectivity than previously developed transition metal catalyzed transformations, thus allowing greater functional group tolerance. One of the most studied branches of research in this fast growing field is the cycloisomerization of enynes.[2] The impressive structural diversity that can be generated and the significant increase in molecular complexity bring enormous synthetic potential to this transformation.[3] One of the greatest challenges in developing cycloisomerization reactions is achieving selectivity between all the possible mechanistic pathways. Pathway divergence is a fascinating aspect of the cycloisomerization reactions that has helped to better understand the mechanistic subtleties of gold(I)-catalyzed reactions and has also provided a perfect platform for the design of new ligands.

The remarkable diversity of cyclic structures that can be accessed from a common 1,6-enyne precursor activated by a soft Lewis acid is highlighted by the large number of possible resonance structures and intermediates accessible. (**Scheme 3.01**).[4] Hypothetically, cyclopropane, cyclobutane, cyclopentane, cyclohexane and even cycloheptane can be generated through this process. The activation of the triple bond of enyne (**3.01**) by a soft Lewis acid will induce a carbon-carbon bond formation via a competitive *5-exo-dig* or 6-*endo-dig* pathway. The 5-*exo-dig* cyclization of substrate (**3.01**) gives metal stabilized homoallylic cation (**3.03**). The resulting cationic intermediate can be depicted by three major resonance forms (**3.03**), (**3.04**) and (**3.05**). The filled *d* orbital of the metal can participate in back bonding to stabilize the cationic charge resulting in cyclopropylcarbene, (**3.04**) or the positive charge can be centered on the alpha carbon in ionic representation (**3.05**).

Both of these reaction intermediates can be trapped in a subsequent reaction.[5] Further skeletal rearrangements of (**3.03**), (**3.04**) and (**3.05**) lead to three different dienes as illustrated by intermediates (**3.06**), (**3.09**) and (**3.10**). Opening of cyclopropyl (**3.05**) can generate another homoallylic carbocation, (**3.17**), where the carbocycle is now a six-membered ring. Products resulting from this mechanistic intermediate are often believed to be the result of a 6-*endo-dig* cyclization since they are similar to the products obtained from the endocyclic pathway such as intermediate (**3.16**). The 6-*endo-dig* cyclization generates cationic intermediate (**3.11**), which can also be represented as a cyclopropyl carbene (**3.14**). However, products resulting from this pathway are generally less common in the literature and appear limited to specific substrates.



Scheme 3.01 *Possible intermediates in metal-catalyzed cycloisomerizations of 1,6-enynes*

3.2 Bonding in gold(I)-catalysis

The reactivity and selectivity exhibited by gold(I) complexes is highly modulated by the nature of the ancillary ligand. Recent research rationalizes the impact of these ligands on the divergent reactivity observed between cationic and carbenoid intermediates.[6] Knowledge of the nature of the bonding and the effect of the electronic properties of the ligand on the metal center in gold(I) intermediates such as (**3.03**), (**3.04**) and (**3.05**) are of paramount importance for the improvement of the selectivity of such catalysts. Toste has suggested that the reactivity in gold(I)-coordinated carbenes are best accounted for by a continuum ranging from a metal-stabilized singlet carbene to a metal-coordinated carbocation.[7] The state of a given gold(I) species on this continuum is largely determined by the substrate functionality as well as the electronic properties of the ancillary ligand. The bonding situation in these carbenoid intermediates has been depicted by three major resonance structures: a vinyl gold(I) homoallylic carbocation (**3.03**), a carbene with a gold–carbon double bond (**3.04**) or a stabilized carbocation with a gold–carbon single bond (**3.05**). After conducting experimental and computational studies, Toste has proposed a bonding model where the carbon–gold bond in these intermediates is comprised, to varying degrees, of both σ- and π-bonding. However, the overall bond order is generally less than or equal to 1 and the π-bonding is the major contribution to the gold(I)-carbon bond. The depiction of a gold-stabilized carbene with a gold–carbon double bond should not be taken as an indication of a bond order of two, but rather a means to indicate that both σ and π components of the bonding are present (**Figure 3.01**).

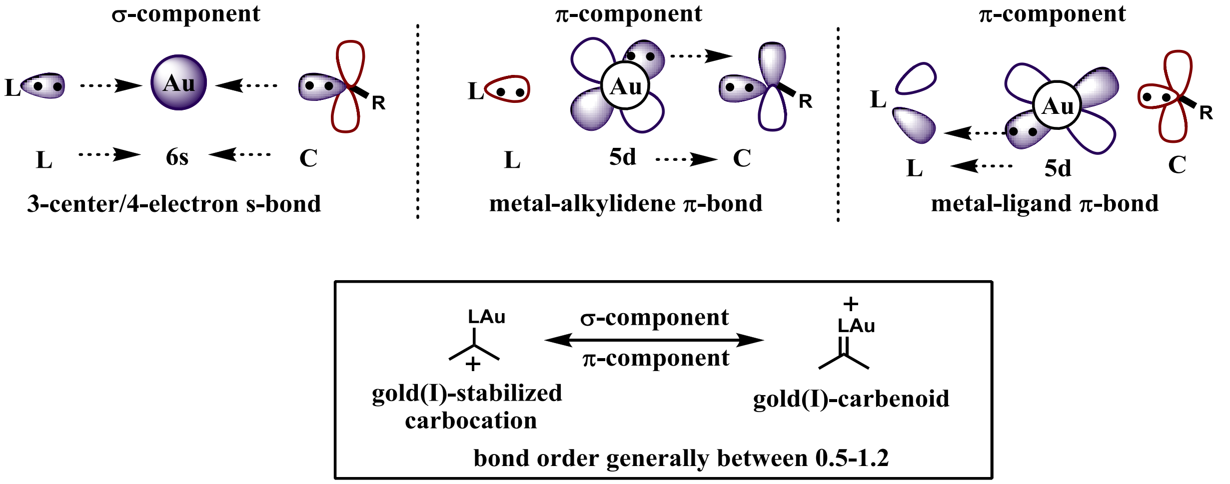


Figure 3.01 *A bonding model for triad ligand-gold–carbene complexes*

The ligand–gold–carbene bonding triad can be divided into three components (**Figure 3.01**). The σ-bonding is mainly composed of a three-center/four-electron hyperbond. This situation results from the Pauli Exclusion Principle and the only vacant orbital on gold being the 6s. The π-bonding consists of electron donation of two orthogonal d orbitals of gold into π–acceptor orbitals of the ligand and/or the carbene. These two bonds compete for electron density and, therefore, have an indirect effect on each other. The bonding model for gold stabilized carbenes shown in **Figure 3.01** proposes that these intermediates possess highly electron-deficient α-carbons that are stabilized, to varying degrees, by back-donation from the metal to the vacant p-orbital of the carbene. This electron deficiency reduces donation from the filled sp^2 hybridized orbital of the carbene to the metal, therefore minimizing gold–carbon σ-bonding. Thus, this model suggests that the conversion of the vinyl-gold intermediate (**3.03**) into a gold stabilized carbene (**3.04**) during a cycloisomerization reaction occurs with an electronic enhancement of the gold–carbon π-bonding and a reduction of the σ-component of the bond.

3.3 General ligand effects in gold(I)-catalysis

The bonding model shown in **Figure 3.01** can be used to predict the effect of the electronic properties of ancillary ligands on the reactivity of related gold(I) complexes. As a consequence of the linear biscoordinate geometry of gold(I) complexes and of the resulting trans effect, strongly σ-donating ligands with neutral or low π-acidity decrease the σ-donation of the gold–carbon bond. This effect increases its bond order and consequently increases the gold-carbon bond length. On the other hand, the π-contribution to the gold-carbon bond reaches a maximum and thereby increases carbene-type reactivity. To date, the best family of ligands possessing these electronic properties are N-heterocyclic carbenes (NHC). The first NHC-Gold(I) complexes were synthesized by Nolan in 1999 and the molecular structure of ligand **IPr** is presented in **Figure 3.02**.[8] NHC ligands are strongly σ-donating, only weakly π-acidic and their gold(I) complexes exhibit excellent carbene-type reactivity such as in cyclopropanation reactions. In contrast, π-acidic ligands are expected to decrease π-donation from the gold to the carbon, thereby increasing carbocation-type reactivity.

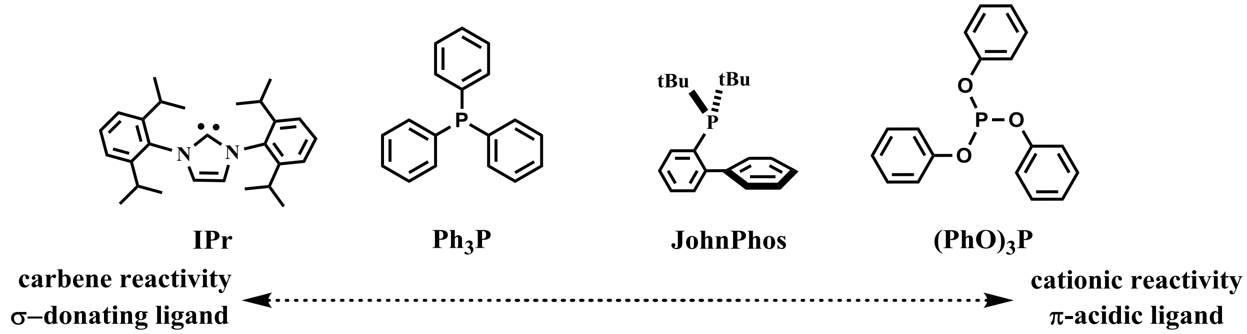


Figure 3.02 *Four ligands used to modulate the electronic property of gold(I) complexes*

A good example of a π-acidic ligand is triphenylphosphite ($(PhO)_3P$) and gold(I) complexes with this type of ligand will favor a more cationic pathway. Phosphine ligands, such as triphenylphosphine (PPh_3), fall between these two extremes.[9]

Bulky biphenyl phosphines based on Buchwald-type ligands, represented by JohnPhos in **Figure 3.02**, promote more cationic pathway than standard phosphines.[10] In these complexes, a weak interaction between the metal and the second phenyl force the ligand–gold–carbon bond angle to divert from the ideal angle of 180°. The geometric distortion of these complexes does not influence the σ-component of the bonding but could decrease orbital overlap between the d orbitals of the gold atom and the empty p orbital of the carbon. This structural feature decreases the stabilization of the cationic charge by the gold(I) complex and thereby disfavors carbenoid reactivity. This last hypothesis, which involves a complementary reactivity between NHC ligands and biphenylphosphine ligands, guided us through most of our research.

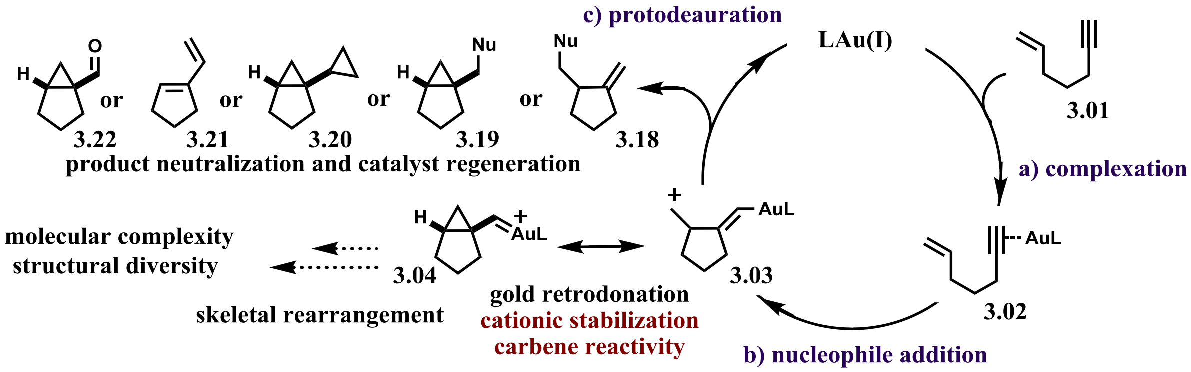
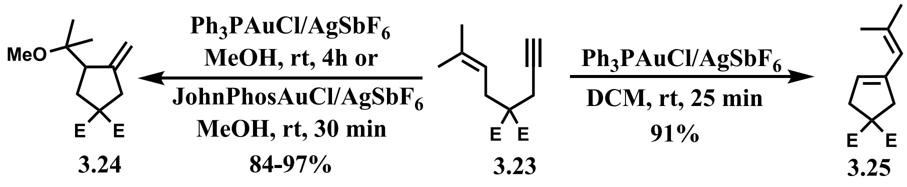


Figure 3.03 *Catalytic cycle of the gold(I)-catalyzed cycloisomerization of 1,6-enynes*

A recent study has demonstrated that the electronic properties of the ligand can also impact the reaction kinetics.[11] A brief analysis of the catalytic cycle will uncover the complexity associated with gold catalysis, as well as demonstrate the importance of understanding the mechanism of the reaction. Most gold-catalyzed reactions undergo through three principal steps (**Figure 3.03**). The first step is (a) complexation of the gold(I)-complex to the alkyne to form π-complex (**3.02**). Kinetic preference is neither encountered in favor of the alkyne nor the alkene; the chemoselective addition of a nucleophile to alkynes but not to alkenes is not based on a preference in the coordination step but on significant differences in the reactivity of these two π complexes. The LUMOs energy levels of alkynes are intrinsically lower than those of alkenes (by ~0.5 eV). The second step is (b) the nucleophilic addition onto the activated complex (**3.02**), generating a vinyl gold intermediate (**3.03**). For cycloisomerization reactions, an intramolecular alkene is used as the nucleophile. The vinyl gold intermediate (**3.03**/**3.04**) can be depicted by two extreme resonance forms which are represented in **Figure 3.03**. Each form has been trapped with an external nucleophile to furnish final products (**3.18**) and (**3.19**).[15,16] In addition, this step is often accompanied by rearrangement of the skeleton where a significant further increase in molecular complexity and structural diversity can be obtained. In some cases, the second step (b) is the rate limiting step and electron deficient ligand on the catalyst will accelerate the reaction by increasing the electrophilic property of the related complex. The final step is (c) the neutralization of the cationic charge by a nucleophile or via proton elimination and protodeauration, which liberates the product and regenerates the active gold catalyst. Contrary to what was initially assumed to be a fast process, protodeauration is often the rate determining step.[12] It was recently demonstrated that an electron rich ligand would accelerate protodeauration and consequently increase the rate of the reaction.[11] It is noteworthy that the electrophilic activation and nucleophilic additions are rarely the rate limiting steps. However, they can be rate limiting steps when weak nucleophiles are used, or during a cationic promoted migration of alkyls or hydrides, or when allenes are used as electrophiles. In the later cases, π-acidic ligands will accelerate the rate of the reaction by forming a more electrophilic complex.[11]

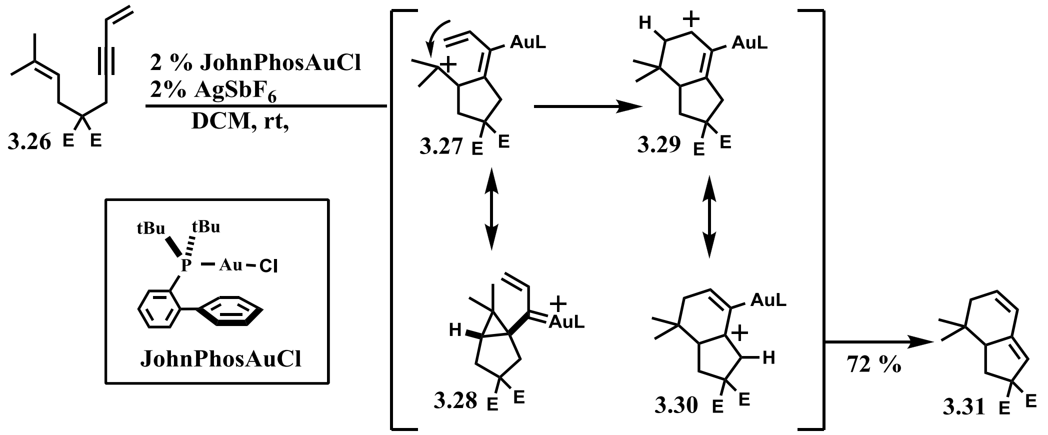
3.4 Ligand effect in the gold(I)-catalyzed cycloisomerization of 1,6 enynes

A staggering diversity of gold(I)-catalyzed skeletal rearrangements have been discovered for substituted and tethered 1,6-enynes with the product distribution generally appearing to be substrate-, rather than catalyst-, dependent.[2] However, some interesting ligand effects have been observed for the cycloisomerization of 1,6-enynes. In 2004, Echavarren reported the cycloisomerization and methoxycyclization of 1,6-enynes of terminal alkynes catalyzed by triphenylphosphinegold(I) complexes (**Scheme 3.02**).[13] Depending on the reaction conditions, either skeletally-rearranged product **(3.25)** or methanol-trapped product **(3.24)** **c**ould be isolated in high yield from the same enyne (**3.23**).



Scheme 3.02 *Echavarren`s cycloisomerization and methoxcyclisation of 1,6-enyne (**3.23**)*

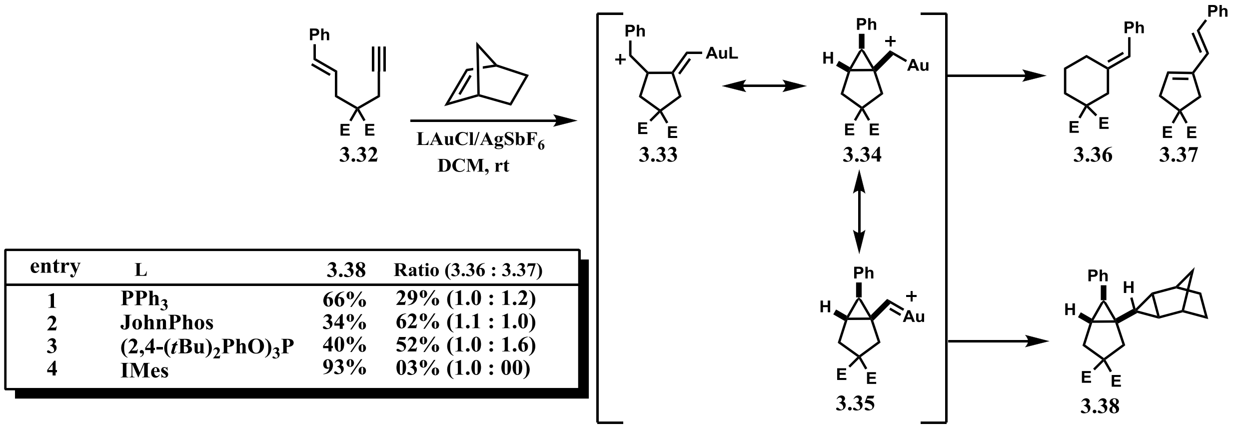
In 2005, Echavarren and co-workers described the synthesis of a series of new gold(I) complexes equipped with Buchwald-type phosphines.[14] These complexes enhance the catalytic activity; the reaction time being up to eight times shorter in the case of the methoxycyclization, affording cyclopentene (**3.24**) over thirty minutes (**Scheme 3.02**). These bulky ligands increase the stability of these complexes resulting in a much slower decay of the active species.[11] These new catalysts were also able to promote a novel process, which corresponded to a formal [4+2] cycloaddition of alkenes with enynes or aryl alkynes to generate products containing an hydrindane framework (**Scheme 3.03**). After an initial carbon-carbon bond formation via a 5-*exo-dig* cyclization, tertiary carbocation (**3.27**) underwent an intramolecular Friedel-Crafts-type cyclization with the diene moiety. The resulting allylic carbocation **(3.29**) can be represented by two resonance forms: (**3.29**) and (**3.30**). Consequently to the positive charge that is more stabilized on the tertiary carbon; the bicyclic diene (**3.31**) was isolated as a sole isomer.



Scheme 3.03 *Echavarren's gold(I)-catalyzed formal [4+2] cycloaddition*

In order to prove the existence of extreme carbene and cationic resonance forms, as depicted by structures (**3.35**) and (**3.33**), trapping experiments have been conducted on the 1,6-enynes (**3.32**) (**Scheme 3.04**).[15] In the case of carbenoid (**3.35**), this intermediate must exhibit reactivity that is similar to that of a free carbene, such as in cyclopropanation reactions. Thus, the intermolecular trapping of the proposed cyclopropyl carbenoid intermediate (**3.35**) with olefins has been investigated. Echavarren has found that the gold(I)-catalyzed cyclization of enyne (**3.32**), using triphenylphosphine (PPh_3**)** as the ligand, gave cycloproponation adduct (**3.36**) as the major product in 66% yield (**entry 1**). Phosphite ligand [$(2,4\text{-}(tBu)_2PhO)_3P$] and biphenyl phosphine ligand JohnPhos exhibited only modest selectivity in differentiating between skeletal rearrangement and intermolecular cyclopropanation pathways (**entries 2** and **3**).

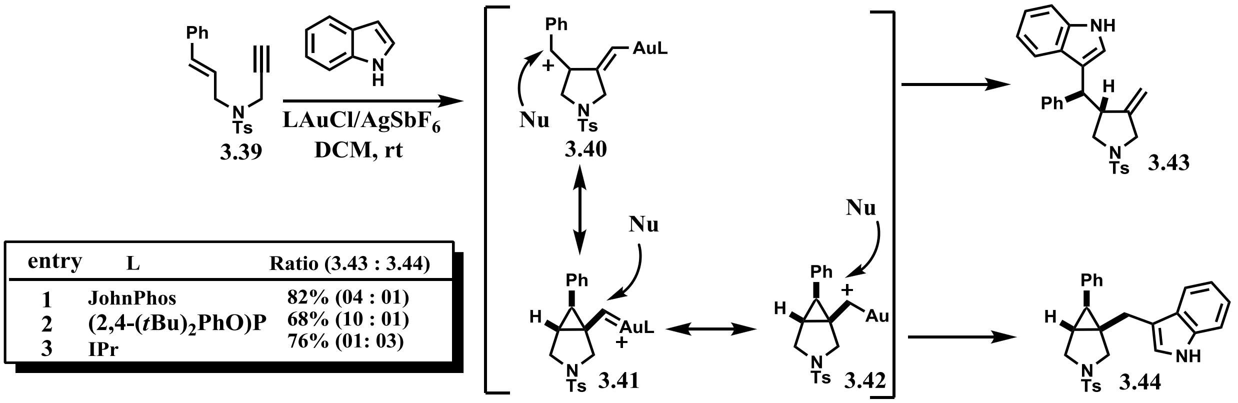
As mentioned previously, steric effects can be responsible of the cationic reactivity of the electron rich JohnPhos phosphine ligand. In contrast, carbenoid reactivity was almost the exclusive pathway when strong σ-donnor NHC ligand IMes was used and afforded the intermolecular cyclopropanation adduct (**3.38**) in 93% yield by trapping with norbornylene (**entry 4**).



entry	L	3.38	Ratio (3.36 : 3.37)
1	PPh_3	66%	29% (1.0 : 1.2)
2	JohnPhos	34%	62% (1.1 : 1.0)
3	$(2,4\text{-}(t\text{Bu})_2\text{PhO})_3\text{P}$	40%	52% (1.0 : 1.6)
4	IMes	93%	03% (1.0 : 00)

Scheme 3.04 *Ligand effect in the cyclopropanation of a cyclopropyl carbene intermediate*

Another interesting study is the intermolecular trapping of 1,6-enynes carried out with indole as nucleophile.[16] Rather than observing ligand-dependent competition between the nucleophilic addition and skeletally rearranged products, Echavarren observed the competitive formation of regioisomeric products arising from the trapping of either homoallyilic cationic vinyl gold intermediate (**3.40**) or cyclopropyl gold(I)-stabilized carbocation (**3.42**). Contrary to the NHC IPr ligand which favor the formation of the cyclopropyl carbenoid adduct (**3.44**), biphenylphosphine JohnPhos and phosphite ligand $(2,4\text{-}(\text{tBu})_2\text{PhO})_3\text{P}$ provided adduct (**3.43**), resulting from the addition of indole to the homoallylic cation (**3.40**), as the major product.

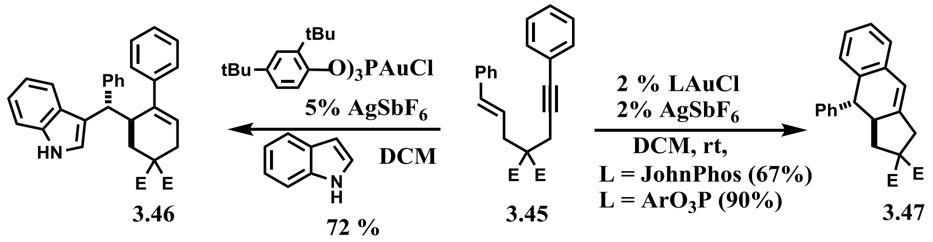


entry	L	Ratio (3.43 : 3.44)
1	JohnPhos	82% (04 : 01)
2	$(2,4\text{-}(t\text{Bu})_2\text{PhO})\text{P}$	68% (10 : 01)
3	IPr	76% (01: 03)

Scheme 3.05 *Ligand effect in the nucleophilic trapping of cationic vinyl gold (**3.40**) and cyclopropyl carbene intermediate (**3.42**)*

3.5 Competitive pathways: 5-exo-dig vs 6-endo-dig cyclization

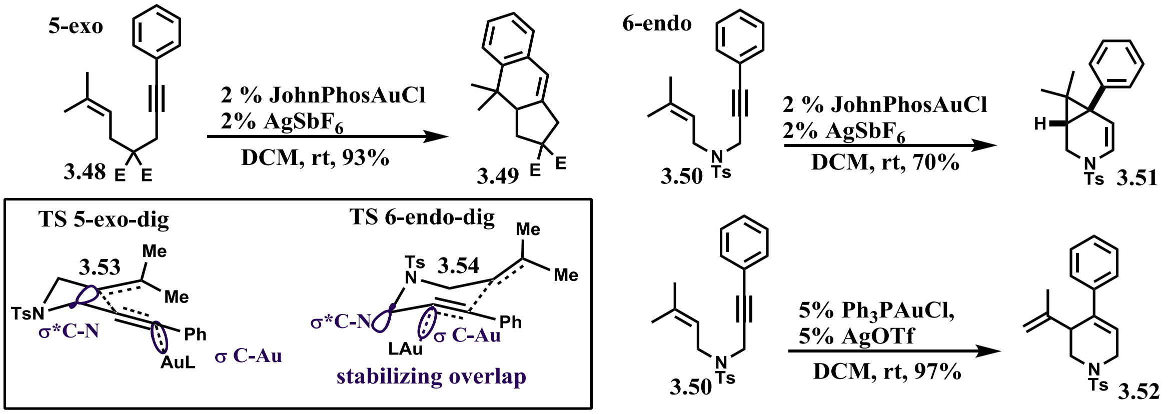
While most recent efforts have tried to understand and control the divergent reactivity of the intermediate resulting from the 5-*exo-dig* pathway, the 6-*endo-dig* pathway has not received the same interest.[17] Although this latter pathway has been encountered in the literature, the narrow reaction scope and the limited influence of the ligand on the outcome of the reactions seemed to restrict severely the use of this reaction in synthesis. However, some interesting examples exploiting the competitive *6-endo-dig* pathway can be found in the gold(I)-catalyzed carbocyclization of 1,6-enynes. Further intermolecular nucleophilic trapping studies on 1,6-enynes were carried out with internal alkynes by Echavarren.[18] Interestingly, the addition of the nucleophile does not trap an intermediate in the formal [4+2] cycloaddition pathway; instead, the indole adds onto an intermediate in the endocyclic pathway to afford cyclohexene (**3.46**). The successful addition of indole to enyne (**3.45**) is quite remarkable because without an external nucleophile, compound (**3.45**) is known to rapidly give tricyclic compound (**3.47**) via an initial 5-*exo-dig* cyclization (**Scheme 3.06**).



Scheme 3.06 *Nucleophilic trapping of intermediate in the endocyclic pathway*

The endocyclic pathway can also be accessed by changing the tether between the alkyne and the alkene. Usually, the tether is used to facilitate the synthesis of the substrate and, at the same time, increase the rate of the cyclization via the Thorpe-Ingold effect. The fact that the tether has an incredible effect on the regioselectivity of the cyclization is more surprising. Compounds (**3.48**) with a malonate linker allow the formation of the formal [4+2] cycloadduct (**3.49**) via the usual 5-exo-dig cyclization, while compound (**3.50**) with a N-tosylamine tether furnish cyclopropyl bicyle (**3.51**).[13,18] Moreover, the use of simple Ph_3PAuCl in the presence of AgOTf provides 6-*endo-dig* cyclization product (**3.52**) in 97% yield. The outcome of the reaction with the N-tosylamine linker can be rationalized by stereoelectronic effects. The addition of nitrogen in the tether is not, as it appears, so innocent; the carbon-nitrogen bond possesses a σ-star orbital of lower energy compare to the orbital of the corresponding carbon-

carbon bond.[19] This empty orbital of lower energy can interact with the newly formed gold-carbon σ-bond, as depicted in the transition state of the 6-*endo-dig* cyclization of compound (**3.54**). Thus, stereoelectronic effects stabilize the transition state of the endocyclic pathway and therefore, change the traditionally observed pathway.



Scheme 3.07 *Stereoelectronic effects favoring the 6-endo-dig over the 5-exo-dig pathway*

These last two examples as well as the development of our synthetically useful 6-*endo-dig* carbocyclization to access PPAP frameworks brought us to reflect on the rules that govern these competitive cyclizations. The Baldwin rules are known to be a concise set of guidelines attempting to rationalize the selectivity observed in competitive cyclizations.[20] Baldwin postulated that ring closures were favored to occur "when the length and nature of linking chains enable the terminal atom to achieve the required trajectories" for the bond formation. Similarly, disfavored reactions are a consequence of severe distortion of bond angles and distances to reach the optimal trajectories. Baldwin suggested that favorable trajectories are dependent on the hybridization of carbons involved in the cyclization. For the addition on sp carbon, the hybridization of our interest, Baldwin proposed an acute angle of attack (**Figure 3.04**). He based his model on the general predominance of *endo* ring closures for diagonal systems in comparison to tetragonal systems. However, the acute angle of attack does not comply with molecular orbital predictions, which suggest an obtuse angle of attack in order to be correctly aligned with the π* orbital of the alkyne.[21] According to higher level calculations, the obtuse angle is indeed the preferred angle, although it varies according to the nucleophile and whether the transition state (T.S.) is considered as an early T.S. (α = ~115°) or a late T.S. (α = ~130°).[22] Thus, a better trajectory for the addition on the alkyne is provided by the obtuse approach, which is analogous to the Burgi-Dunitz trajectory for addition on a carbonyl.

These findings also corroborate stereoelectronic considerations as the obtuse approach minimizes interaction of the incoming nucleophile with the nodal plane of π*-orbital. When these considerations are put in the context of an intramolecular digonal cyclization, the obtuse angle of attack would imply stereoelectronic preference for the *exo* trajectory over the *endo* trajectory.

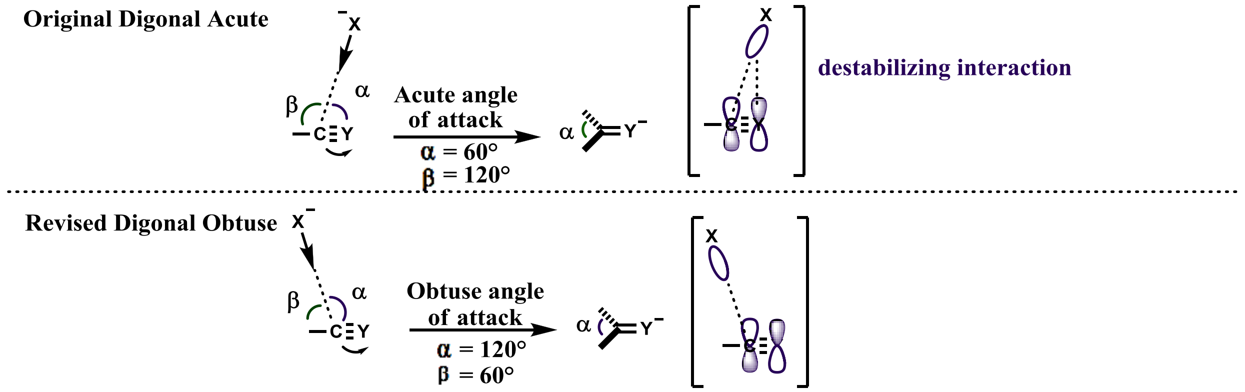


Figure 3.04 Baldwin's original and revised geometry of nucleophilic additions on sp carbon

As the ring size increases, the obtuse angle of attack in an *endo*-type cyclization becomes more favorable and starts to compete with the *exo*-type cyclization; this is the case for *6-endo-dig* processes although *5-exo-dig* cyclizations are typically preferred. On the other hand, thermodynamic considerations should favor the 6-*endo-dig* cyclization.[23] Thermodynamic contributions are not negligible even when reactions proceed under kinetic control. In fact, thermodynamic factors may relax stereoelectronic requirements therefore modifying kinetic predispositions of the Baldwin rules. Based on Marcus' theory, favorable thermodynamic contributions can effectively reduce the activation energy of a process, it is nonetheless inappropriate to compare the preference of the nucleophile's trajectories of two processes (*exo vs endo*) when their exothermicities are different.[24] This can effectively happen during the formation of an aromatic six-membered ring. Structural aspects have a tremendous impact on the predisposition of a molecule to undergo *5-exo* or *6-endo-dig* cyclizations. Internal strain also plays an important role in the case of fused ring systems. It is also noteworthy that the *6-endo-dig* cyclization will generally be preferred when the cyclization product contains internal strain.[25] While intrinsic stereoelectronic preferences for *exo*-dig ring closures can be overshadowed by additional factors, such as polarization of the π-system and thermodynamic effects, substrates including these bias factors will not be discussed in the following selected examples of 6-*endo-dig* cyclizations.[26]

3.6 Gold(I)-catalyzed Conia-ene reaction

The representation of pentynyldimalonate (**3.61**) in its enol form illustrates the close proximity of the Conia-ene reaction with the cycloisomerization of 1,6-enynes (**Figure 3.05**). The Conia-ene reaction is an intramolecular thermal or Lewis acid catalyzed Ene reaction of unsaturated ketones, in which the carbonyl functionality serves as the ene component, via its enol tautomer, and the olefinic moiety serves as the enophile. Readily enolized β-ketoesters were used in this reaction and later, the corresponding silyl enol ethers were used as well. However, thermal Conia-ene reactions usually require harsh conditions, thus the racemization of the product and/or the isomerization of the exo olefin can occur, when it is not just the decomposition of the starting material. The thermal version was discovered by Conia in the late 1960’s and was initially proposed to proceed via a concerted pericyclic transition state.[28]

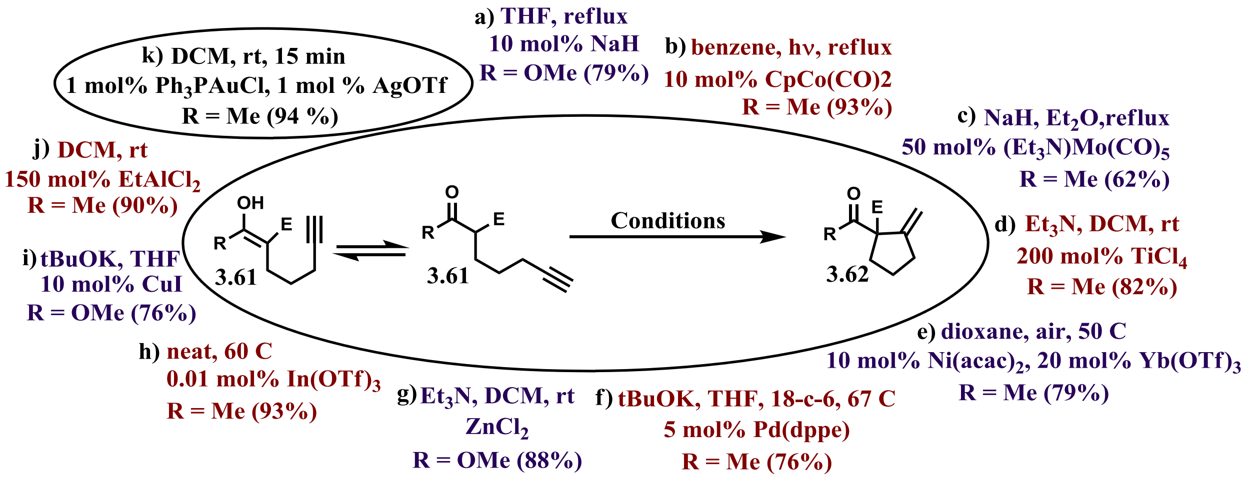
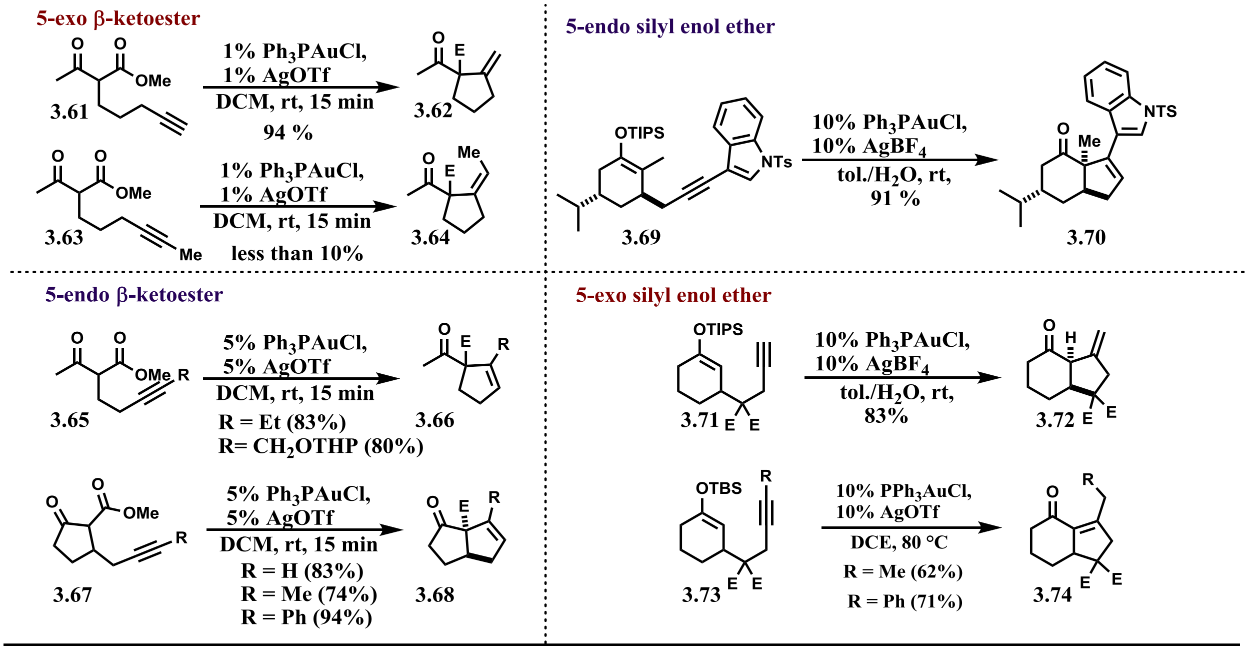


Figure 3.05 *Resume of catalysts used for the 5-exo-dig Conia-ene cyclization of terminal alkyne tethered β-ketoesters*

Recently, a number of metal-catalyzed reactions that are carried out under mild conditions have been devised for the preparation of carbocycles (**Figure 3.05**).[29] On a simple substrate such as pentynylmalonate (**3.61**), catalytic deprotonation with sodium hydride in refluxing THF allowed the transformation and afforded the cyclopentene (**3.62**) in 79% yield (**condition a**).[29a] Stoichiometric formation of aluminum, titanium or zinc enolates also produced cyclization product (**3.62**) (**condition d, g and j**).[29d,j,i] Malacria and coworkers reported that under photolysis conditions, in refluxing benzene, CpCo(CO)$_2$ promoted the 5-*exo-dig* carbocyclization of (**3.61**) (**condition b**).[29b] Under basic conditions, a variety of other metals such as Mo(II), Cu(I) and Pd(0) also catalyzed the Conia-ene reaction of β-ketoester (**3.61**) (**condition c, f and i**).[29c,f,i] Milder reaction conditions were developed using Ni(II)/Yb(III), In(III) or Au(I) catalysts (**condition e, h and k**).[29e,h,k]

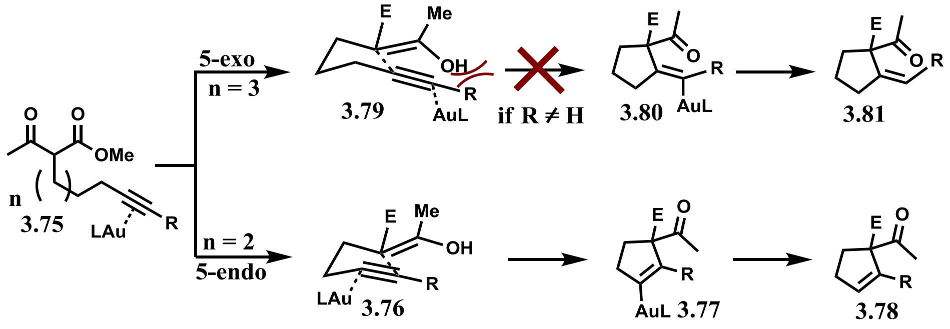
In 2004, Toste's group reported the gold(I)-catalyzed Conia-ene cyclization of various β-ketoesters for the synthesis of cyclopentenes via two modes of cyclization: 5-*endo-dig* and 5-*exo-dig* carbocyclization (**Scheme 3.08**).[29k] To their delight, triphenylphosphinegold(I) chloride with silver triflate catalyzed the cyclization of β-ketoester (**3.61**) and provided cyclopentene (**3.62**) over 15 minutes in 94% yield with only 1% catalyst loading. The 5-*endo-dig* cyclization needed more catalyst loading (5%), but substitution at the end of the triple bond was well tolerated, affording cyclopentenes (**3.66**) or bicyclopentenes (**3.68**) in good to excellent yields.



Scheme 3.08 *Gold(I)-catalyzed Conia-ene reaction of β-ketoester and silylenol ethers*

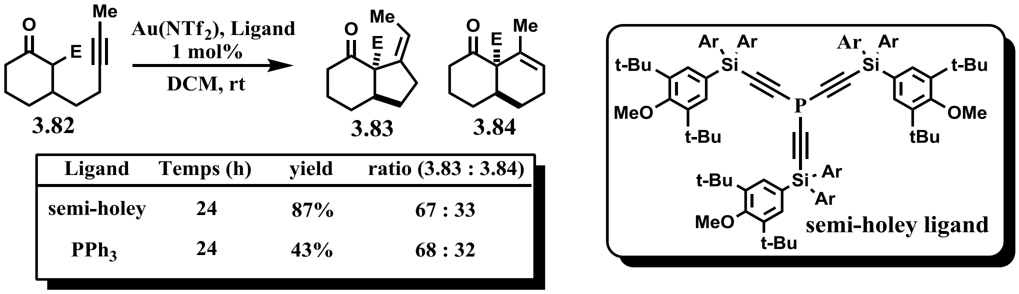
However, the 5-*exo-dig* cyclization of non-terminal alkynes produced less than 10% of the desired cyclopentene (**3.64**). Two years later, Toste and coworkers reported that, with an increase in catalyst loading, silyl enol ethers (**3.69**) and (**3.71**) could be used as nucleophile.[30] Finally in 2007, Lee and Lee demonstrated that heating enables the 5-exo-dig cyclization of internal alkynes and isolated in modest yield bicycle (**3.74**), which had undergone an olefin isomerization and conjugation to the ketone.[31] Toste has proposed that these reactions proceed via nucleophilic addition of the enol moiety onto the gold(I)-activated alkyne (**Scheme 3.09**). They validated the *trans*-addition mechanism using alkyne (**3.79**) to generate deuterium labeled cyclopentene (**3.81**).

They also proposed that the development of 1,3-allylic strain in the transition state of the 5-*exo-dig* cyclization of (**3.79**) explained the sluggish reactivity of internal alkynes. This strain is absent in the transition state for the gold(I)-catalyzed 5-*endo-dig* cyclization of (**3.76**), thus allowing the efficient participation of disubstituted alkynes.



Scheme 3.09 *Toste's mechanistic proposal for the gold(I)-catalyzed Conia-ene reaction*

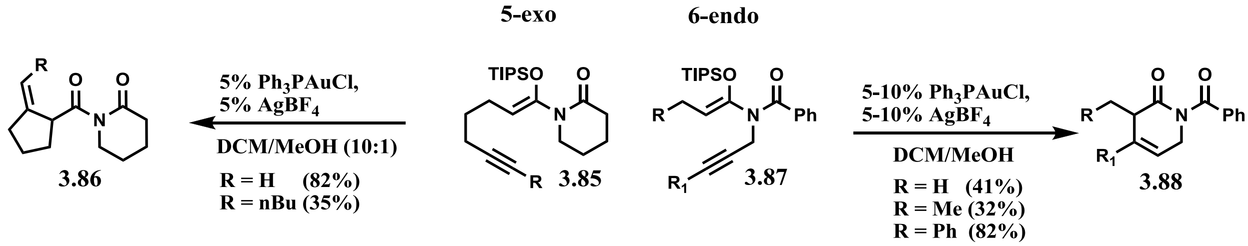
In 2006, Sawamura observed great rate accelerations when triethynylphosphinegold(I) catalysts (semi-holey ligand) were used in 6-*exo-dig* carbocyclizations.[32] It was proposed that a decrease in the activation entropy, enforced by the holey catalytic environment of the ligand, was the source of the enhanced catalytic activity of this catalyst. Later in 2008, they successfully used the semi-holey ligand in the cyclization of challenging non-terminal alkyne (**3.82**) via a 5-*exo-dig* or 6-*endo dig* cyclization and observed a 2:1 ratio in favor of the 5-*exo-dig* product (**Scheme 3.10**).[33] A control reaction using triphenylphosphine (PPh_3) as the ligand demonstrated that this transformation occurs with the same regioselectivity, albeit in lower yield. The triflimide (NTf_2) anion, used by Sawamura and initially developped in gold catalysis by Gagosz, generally behaves similarly to other weakly and non-coordinating counterions while offering greater air stability.[34]



Ligand	Temps (h)	yield	ratio (3.83 : 3.84)
semi-holey	24	87%	67 : 33
PPh_3	24	43%	68 : 32

Scheme 3.10 *Rate acceleration of the gold(I)-catalyzed Conia-ene reaction by semi-holey ligand*

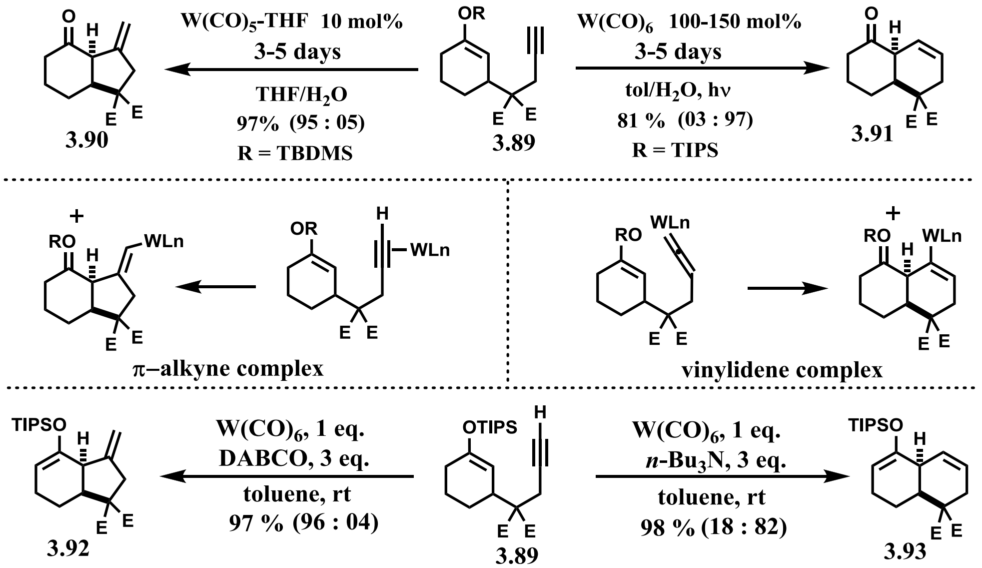
In 2007, researchers from Merck in collaboration with Dean Toste, reported an interesting gold(I)-catalyzed regioselective cyclization of silyl ketene amides and carbamates with alkynes (**Scheme 3.11**).[35] They observed that the design of the substrate greatly influenced the regioselective outcome of the reaction. Depending on the position of the nitrogen atom, exclusive formation of 5-membered or 6-membered rings was observed. Presumably due to stereoelectronic requirements and stabilization (**see Scheme 3.07** for explanation), terminal amides or carbamates bearing appended alkynes cyclized via a 5-*exo-dig* mode, whereas a 6-*endo-dig* cyclization process was observed for substrates containing a C-N linker. The 5-*exo-dig* cyclization was easier with terminal alkynes while the 6-*endo-dig* cyclization worked well with phenyl substitution on the alkyne.



Scheme 3.11 *Substrate dependent regioselective 5-exo-dig or 6-endo-dig carbocyclization*

3.7 Tungsten-catalyzed Conia-ene reaction

As mentioned briefly in **Section 2.3**, Iwasawa and co-workers made great contributions to the field of alkyne π-activation and their subsequent reactivity as electrophiles.[36] Their studies were predominantly devoted to the reactivity of a photo-activated tungsten catalyst, $W(CO)_5$•THF, which is prepared by irradiating $W(CO)_6$ with a mercury lamp. This group reported the cyclization of a wide range of silyl enol ethers and was an inspiration for our work: a milestone to surpass. For almost all types of cyclizations, reducing the catalyst loading from 1.5 equivalent to 10 mol % had little influence on the chemical yields, although the reaction was much slower (5-7 days vs 1-2 days). Interestingly, this tungsten-catalyzed cyclization was found to be highly dependent on the solvent which complexes to the catalyst. The regioselectivity could be reversed by replacing THF with a less donating solvent such as toluene and generating the catalyst *in situ*.



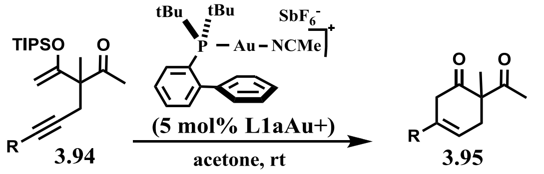
Scheme 3.12 *Tungsten-catalyzed selective synthesis of fused carbocycle*

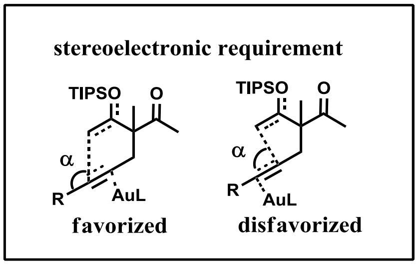
While the cyclization of (**3.89**) in THF led to the regioselective formation of 5-membered ring (**3.90**), the preparation of 6-membered ring from (**3.89**) via a regioselective 6-*endo* cyclization process was achieved by carrying out the reaction in toluene.[37] In this case, the catalyst loading could not be decrease below the stoichiometric amount. The perfect regioselective control of the cyclization was accomplished by the differentiation of two distinct mechanistic pathways. A classic complexation of the triple bond led to the π-alkyne complex, which underwent a 5-*exo-dig* cyclization. With the other set of condition, a vinylidene complex resulted from the complexation of the alkyne by the catalyst. The electrophilic carbon was now the one attached directly to the metal, favoring the 6-endo-dig carbocyclization. Previous experiments using deuterium labeling have shown that these two distinct mechanistic pathways were in competition.[38] However, this catalytic system has several drawbacks: it has high catalyst loading and long reaction times, a result of the low catalytic activity. Moreover, the catalyst needs to be activated by irradiation and only limited substitutions are tolerated on the alkyne (iodide and hydrogen). It is noteworthy that tertiary amines could also be used as additives in order to control the regioselectivity of the cyclization process for reactions carried out in toluene under irradiation.[39] When THF was used as a solvent, the nature of the base had only a minor influence on the regioselectivity, but in toluene, the nature of the amine dramatically influenced the regioselective outcome of this tungsten-mediated cyclization (π-alkyne complex vs.vinylidene complex).

Bulky tertiary amines such as *n*Bu$_3$N were the best bases in order to retain the vinylidene pathway, while DABCO steered the reactivity towards the 5-*exo-dig* pathway leading to silyl enol ether (**3.90**).

3.8 Substrate exploration towards a general 6-endo-dig carbocyclization

The previous section demonstrated that the reactivity and selectivity of gold(I)-catalyzed cycloisomerizations may be tuned by switching the ancillary ligand on the cationic gold(I) complex (**Figure 3.02**). Moreover, biphenylphosphine ligands such as JohnPhos (**L1a**) bring unique reactivity to gold(I) catalysis and tolerate well disubstitutions on the alkyne. We therefore started a program to study the impact of this ligand on the regioselectivity of the cyclization of internal alkynes in order to develop a gold-based route to synthetically useful decalin systems. We began our investigation with substrates that we now recognize as substrates biased since stereoelectronic effects predisposed them to undergo a 6-*endo-dig* cyclizations. Treatment of linear silyl enol ethers (**3.94a-c**) with cationic JohnPhosgold(I) complex (**L1aAu+**) provided the corresponding cyclohexenes in high yields and as sole isomer, even on terminal alkyne (**3.95a**). The reaction conditions were mild and no conjugated enones, resulting from double bond migration, were observed. Phenyl and, more interestingly, vinyl substituents were tolerated on the alkyne (**3.94b-c**).





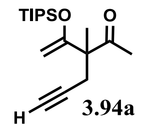
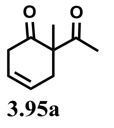
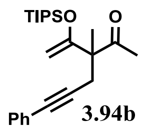
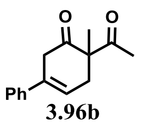
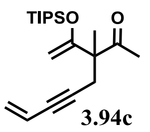
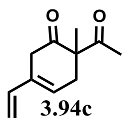
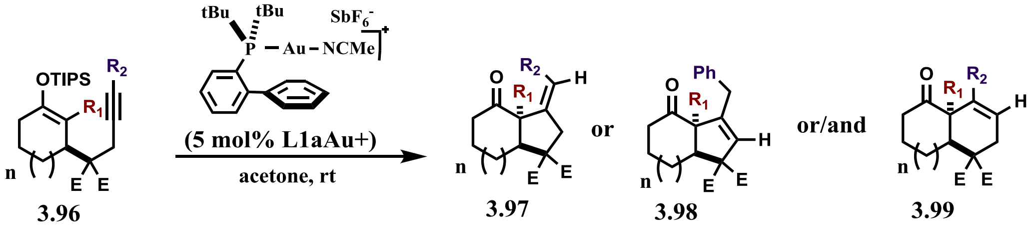
entry	substrate	product	yield
1	 3.94a	 3.95a	93%
2	 3.94b	 3.96b	92%
3	 3.94c	 3.94c	91%

Table 3.01 *Scope of the 6-endo-dig carbocyclization of linear silyl enol ethers*

Next, we explored the cyclization with ring templates in order to access decalin systems such as compound (**3.99**). We synthesized nine different silyl enol ethers (**3.96a-i**) based on two cyclic templates. We changed the ring size, the substitution on the alkyne and the substitution alpha to the ketone for the creation of a vicinal quaternary center. The cyclization of terminal alkyne (**3.96a**) using cationic JohnPhos gold(I) complex (**L1aAu+)** furnished bicycle (**3.97a**) as a single product in 92% yield (**Table 3.02, entry 1**). Disappointingly, no traces of decalin **(3.99a**) were detected. On the other hand, phenyl (**Ph**) substitution on the alkyne reversed the regioselectivity almost completely in favor of the desired 6-*endo-dig* bicyclic product (**3.99b**). This result was in sharp contrast to the one reported by Lee and Lee who only obtained a moderate yield of the 5-*exo-dig* bicycle (**Scheme 3.09**).[31] Moreover, Lee and Lee observed the conjugation of the alkene with the ketone under their conditions.

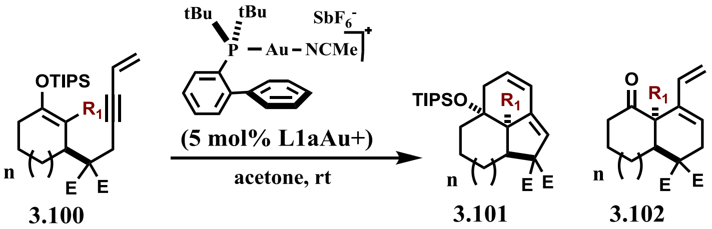


entry	substrate	R1	R2	n	yield (3.97/3.98 : 3.99)
1	3.96a	H	H	1	92% (100 : 00)
2	3.96b	H	Ph	1	88% (10 : 90)
3	3.96c	H	Me	1	91% (57 : 43)
4	3.96d	Me	Ph	1	87% (51 : 49)
5	3.96e	Me	Me	1	89% (90 : 10)
6	3.96f	H	Ph	0	86% (64 : 36)
7	3.96g	H	Me	0	86% (87 : 13)
8	3.96h	Me	Ph	0	89% (16 : 84)
9	3.96i	Me	Me	0	93% (69 : 31)

Table 3.02 *Scope of the 6-endo-dig carbocyclization of cyclic silyl enol ethers cyclic template*

As our conditions are milder, we did not observe any isomerization of the double bond with terminal alkynes (**H**) or methyl (**Me**) substituted alkynes (**entries 1** and **3**). However, when phenyl (**Ph**) substituted alkynes were submitted to the reaction conditions, only the isolation of the internal alkyne (**3.98**) was observed **(entry 2).** Even when the later reaction was performed and monitored by NMR, the external alkene was not detected. Unfortunately, a dramatic erosion of the selectivity was observed when a methyl **(Me)** substituent was present on the triple bond and only a (57: 43) ratio in favor of hinderane bicyclic compound (**3.97c**) was obtained (**entry 3**). The addition of a methyl alpha to the ketone (R1=**Me**) disfavors the 6-*endo-dig* pathway on the six-member ring template. Even when R2 was a (**Ph**), roughly a 1:1 mixture was obtained (**entry 4**). Moreover, a good selectivity in favor of the undesired bicyclic compound (**3.97e**) was achieved when R2= **Me** (**entry 5**). We then performed the same exercise with the 5-member ring template. Interestingly, the R1 substituent had the reverse regioselective outcome for 5-membered rings as opposed to 6-membered rings. While 5-member ring tetra-substituted silyl enol ethers (**3.96h**) (R1=**Me**) favored the 6-*endo-dig* pathway, the tri-substituted silyl enol ethers (**3.96f**) (R1=**H**) were more predisposed to undergo 5-*exo-dig* cyclizations (**entries 6** and **8**). With a methyl on the alkyne (R2 = **Me**), we can observe the same tendency, but the 5-*exo-dig* pathway is more predominant (**entries 7** and **9**). This quick study shows us that the regioselective outcome is strongly substrate dependent. General guidelines may be deduced: phenyl **(Ph)** substituent at R2 favors the *6-endo-dig* pathway more than the methyl (**Me**) substituent. On the 6-member ring template, addition of a methyl (**Me**) alpha to the ketone allows the 5-*exo-dig* cyclization to become the major pathway. This last conclusion is inversed on 5-membered ring templates, where the 6-*endo-dig* pathway is increase when R_1 is a methyl (**Me**). We selected substrate (**3.96f**) as an ideal model to perform a ligand effect investigation in order to improve the selectivity in favor of the 6-*endo-dig* product (**3.99f**). This compound was chosen because it gave the undesired 5-*exo-dig* compound as the major product, thus allowing considerable selectivity improvement. While this compound was not the most selective substrate towards the undesired product, detection of the mixture by ^{1}H-NMR analysis was easier due to the different chemical shifts exhibited by the olefinic protons of compounds (**3.98f**) and (**3.99f**).

Before the optimization of the regioselectivity, we wondered whether this reaction would be tolerant of enynes and if we could achieve good selectivity for the 6-*endo-dig* pathway with these types of substrates. The synthetic potential of generating dienes towards a practical synthesis of complex steroid cores as well as related diterpenes was one of our major goals when we start this research. The cyclization of enyne (**3.100a**) using cationic JohnPhosAu(I) (**L1aAu+)** was attempted in acetone and provided a mixture of two products: the desired product was the minor one (**3.013a**), while the major product (**3.101a**) was the result of a *5-exo-dig* cyclization followed by a Prins cyclization (**Table 3.03**, **entry 1**). This gold(I)-catalyzed formal [4+2] cycloaddition had previously been reported by Echavarren and coworkers and the mechanism is depicted in **Scheme 3.03**. When the substituent at the ring junction R1 was a methyl (**Me**), exclusive selectivity was obtain for the formal [4+2] product, either for the 5- or 6-membered ring template (**entries 2-4**). To our delight, the 6-*endo-dig* pathway did not proceed further to undergo a Prins-type cyclization. Thus, a proof of concept in the generation of useful diene was achieved, albeit with modest selectivity.



entry	substrate	R1	n	yield
1	3.100a	H	1	88% (66 : 34)
2	3.100b	Me	1	85% (100 : 0)
3	3.100c	H	0	81% (88 : 12)
4	3.100d	Me	0	67% (100 : 0)

Table 3.03 *Substrate exploration towards a general 6-endo-dig carbocyclization: vinyl substituent*

Pionnering work by Echavarren has brought new insight in the unique reactivity of the biphenylphosphine ligand JohnPhos (**L1a**) in gold(I) catalysis. As is now experimentally shown, the JohnPhos ligand (**L1a**) increases the stability and the reactivity of the gold(I) complex.[40] The decay of the active species is slower and protodeauration is accelerated, providing better efficiency for challenging reactions. One of the first impacts of this outstanding reactivity was its use in the cyclization of internal alkynes as well as the discovery of new reactivity. Biaryldialkyl phosphines, particularly those developed by the Buchwald group, have attracted much attention for their efficiency in mediating palladium catalyzed C–C, C–N and C–O bond formations.[41] Moreover, several ligands are commercially available and research by the Buchwald group has led to a wide family of biarylphosphine ligands with distinct steric and unique electronic properties. However, contrary to Pd(0)-catalysis, no general and comprehensive exploration had been conducted for Au(I)-catalysis. The evaluation of this family of ligands in gold catalysis represented a great opportunity to improve the selectivity of those catalysts. The scope and limitations of this process with the JohnPhosAu(I) catalyst (**L1aAu+**) provided us a standard to bear in mind in terms of substrate-selectivity bias.

3.9 Ligand screening and scope of the selective gold(I)-catalyzed synthesis of fused carbocycles

As our goal was to perform a comprehensive screening of the ligand effect in the regioselectivity of the carbocyclization, we started our investigation with PPh_3 ligand and electron richer Et_3P ligand. As anticipated, triphenylphosphine (PPh_3) was a poor ligand choice for both yield and *endo*-selectivity. Triethylphosphine (Et_3P) increased the yield to 70% but kept the regioselectivity preference in favor of the 5-*exo-dig* product (**3.98**) with a ratio of 86:14. We had already found that Buchwald-type phosphines such as JohnPhos (**L1a**) improved both efficiency and the *endo*: *exo* ratio. With the intention of increasing steric bulk, we first screened the two other substituents on the phosphine. In this way, the adamantyl analogue of JohnPhos **(L1b)** was tested and to our great surprise, the *endo*: *exo* ratio was the lowest in this series. One could assume that if adamantyls are not bulkier than *tert*-butyls, they would at least offer similar steric bulk. We also made the cyclohexyl (**L1c**), phenyl (**L1d**), mesytyl (**L1e**) and 4-methoxyphenyl (**L1f**) analogues. These ligands gave similar results with regard to the regioselectivity. Interestingly, the mesityl substituent offers comparable selectivity to *tert*-butyl. In short, adamantyl (**L1b**) are the least selective for endo cyclization, followed by aryl groups that do not provide steric bulk (**L1d-f**), followed by cyclohexyl (**L1c**) and then mesityl (**L1e**) / *tert*-butyl (**L1a**) was quite equivalent. We then investigated other commercially available Buchwald ligands such as Xphos **(L2c)** and tBuXPhos **(L2a)**. With these bulkier ligands, inversion of the selectivity when compared to JohnPhos **(L1a)** was achieved favoring the 6-*endo-dig* product in approximately a 3:2 ratio. We then looked at both BrettPhos **(L3c)** and JackiePhos (**L3g**), which embed two methoxy groups on the first aryl. BrettPhos **(L3c)** gives similar selectivity compared to tBuXPhos **(L2c)** but electron poor version JackiePhos **(L3g)** switches back the 5-*exo-dig* cyclization as the major pathway**.** DavePhos (**L4c-d**) as well as RuPhos **(L5c)** gave ratios similar to the JohnPhos analogues (**L1a-f)**. TrixiePhos (**L6a**) gave a respectable ratio of 41:59 favoring the 6-*endo* product **(3.99f)**.

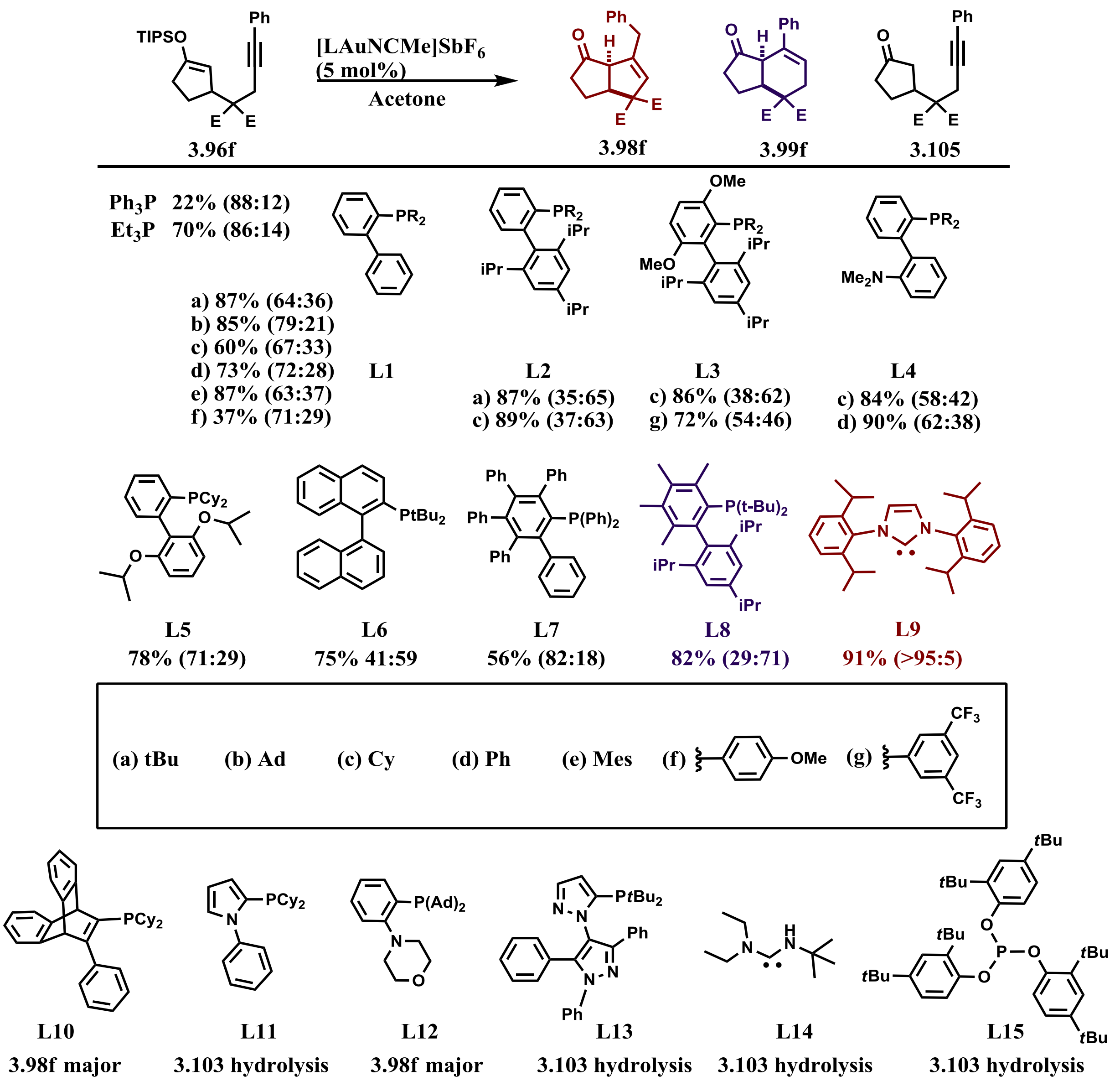


Table 3.04 *Ligand impact on the regioselectivity of the gold(I)-catalyzed carbocyclization*

Furthermore, the new polyphenylphosphine ligand (**L7d**) gave a lower yield and a ratio comparable to the non-Buchwald-type phosphines (**PPh$_3$** and **PEt$_3$**). X-ray analysis demonstrated that this ligand is too sterically hindered for the arene stabilization with the gold(I) metal to occur.[42] Finally, using Me$_4$tBuXPhos (**L8a**) we found the best result in this ligand series with a ratio of 29:71 favoring 6-*endo-dig* product **(3.99f)**, altogether with a good yield of 82%. We also looked at N-heterocyclic carbene (NHC) ligand as IPr (**L9**) and were pleased to discover that this strongly σ-donating ligand is very selective for the *5-exo-dig* cyclization pathway, furnishing bicycle **(3.98f)** in exquisite selectivity.

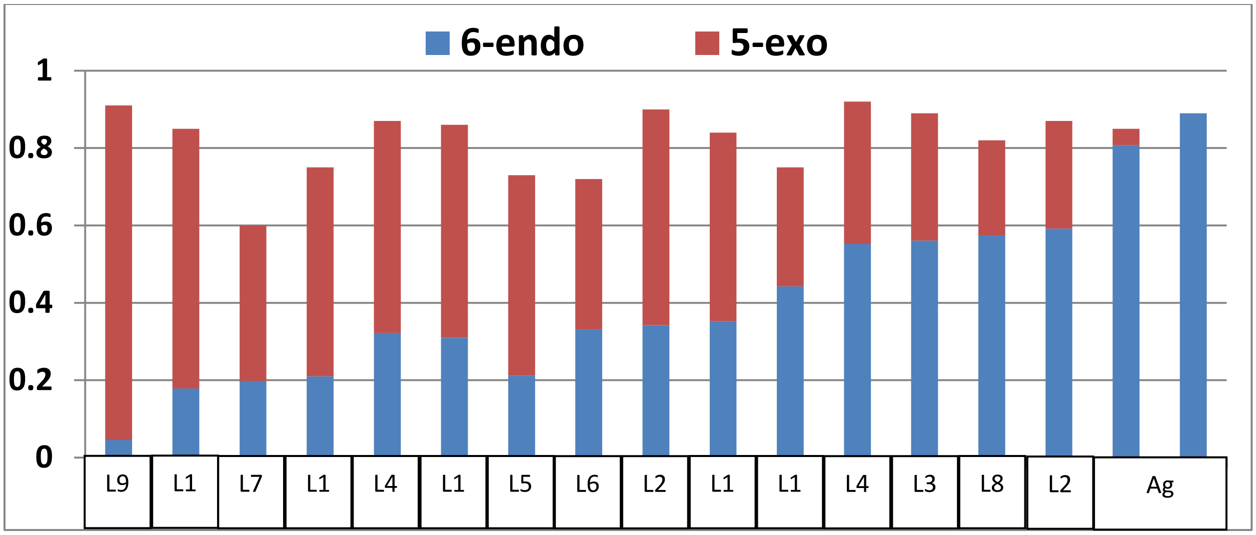
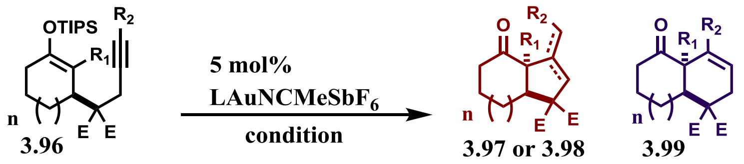


Figure 3.06 *Summary of the ligand impact on the regioselectivity of the gold(I)-catalyzed carbocyclization*

It is important to note that (**L1b**), (**L1d**), (**L1e**), (**L1f**) and (**L7**) and related cationic gold(I) complex were synthesized by M. Sc. Student Patrick Levesque. Our results are summarized in **Figure 3.06** and we can observe our slow progression toward a more selective 6-*endo-dig* carbocyclization. Moreover, it should be mentioned that the two last examples named **Ag**, where better selectivity for the 6-*endo-dig* pathway is obtained, were not discussed. These results were obtained with a silver(I) catalyst and will be discussed in detail in chapter 5. With these results in hand, we explored other substrates aimed at extending the scope of the 6-*endo-dig* carbocyclization. Moreover, both sets of ligands, NHC ligands and biphenylphosphine ligands, have exhibited complementary reactivity in gold(I)-catalysis and have modulated the selectivity amongst competing reaction pathways. Finally, the other objective was to observe if our two selected ligands Me_4tBuXPhos (**L8a**) and IPr (**L9**) can overcome the privileged cyclization pathway determined by intrinsically structural features.

Exploring the impact of these ligands on the outcome of the regioselectivity begins with the new investigation of the substrates in **Table 3.02.** The use of IPr ligand (**L9**) and Me4tBuXPhos ligand (**L8a**) bring now useful selectivity in the competitive 5-*exo-dig* and the 6-*endo-dig* carbocylization pathways (**Table 3.05**). Previously, with JohnPhos **(L1a)**, the eight different substrates (**3.96a-e**) have been demonstrated to give mostly an unselective mixture of the two products (**3.97** or **3.98**) and (**3.99**); while only three products have been synthesize selectively (**3.99b**), (**3.97e**) and (**3.97g**).



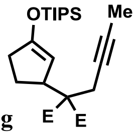
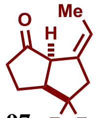
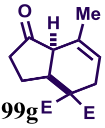
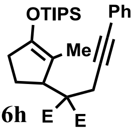
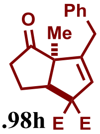
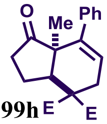
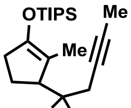
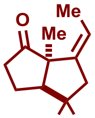
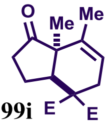
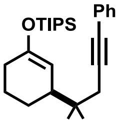
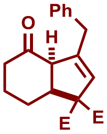
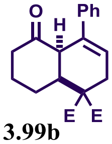
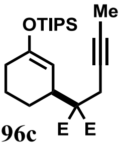
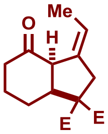
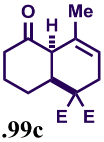
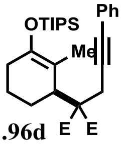
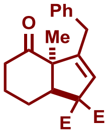
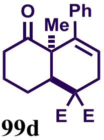
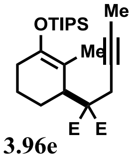
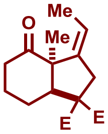
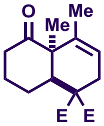
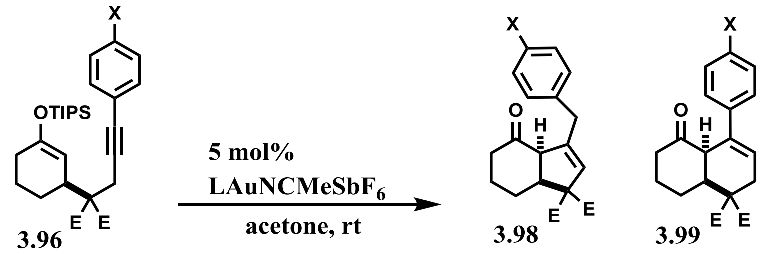
entry	substrate	ligand(condition)	product	yield (ratio)
1	 3.96g	IPr, acetone, rt	 3.97g  3.99g	86% (≤ 95 : 5)
2		Me$_4$XPhos DCM, -10 °C		69% (45 : 55)
3	 3.96h	IPr, acetone, rt	 3.98h  3.99h	88% (48 : 52)
4		Me$_4$XPhos acetone,rt		86% (13 : 87)
5	 3.96i	IPr, acetone, rt	 3.97i  3.99i	94% (92 : 08)
6		Me$_4$XPhos DCM, -10 °C		83% (07 : 93)
7	 3.96b	IPr, acetone, rt	 3.98b  3.99b	86% (40 : 60)
8		JonhPhos acetone, rt		88% (10 : 90)
9	 3.96c	IPr, acetone, rt	 3.97c  3.99c	88% (87 : 13)
10		Me$_4$XPhos DCM, -10 °C		60% (23 : 77)
11	 3.96d	IPr, acetone, rt	 3.98d  3.99d	87% (86 : 14)
12		Me$_4$XPhos acetone,rt		91% (29 : 71)
13	 3.96e	IPr, acetone, rt	 3.97e  3.99e	86% (≤ 95 : 5)
14		Me$_4$XPhos DCM, -10 °C		58% (62 : 38)

Table 3.05 *Scope of the regioselective gold(I)-catalyzed 5-exo-dig and 6-endo-dig carbocyclization*

However, using NHC IPr (**L9**) and the bulky Me$_4$tBuXPhos **(L8a)**, twelve of sixteen products can be selectively synthesized. The four remaining examples show the limitations of the identified ligands. In only one example (out of eight), the desired 6-*endo-dig* compound was not the major product (**entry 14**). Thus, 5-5, 5-6, 6-5 and 6-6 member rings within fused systems can be selectively synthesized and formation of an interesting angular methyl at the ring junction is well tolerated during the cyclization of both processes. When a methyl (**Me**) substituent on the alkyne was tested, the 6-*endo-dig* was found to be more challenging in acetone. Fortunately, we found that slightly wet DCM gives better regioselectivity and we were able to obtain excellent selectivity for (**3.99i**) (**entry 6**). Substrates (**3.96g**) and (**3.96e**) under the same conditions disappointingly give poor selectivity and a reduction of the isolated yield was also observed (**entries 2** and **14**). The cyclization process is not less efficient, but the formation of a new and chromatographically separable product explains the diminution of the yield. This specific case will be discussed in more detail in chapter 5. However, the two substrates (**3.96b**) and (**3.96h**) with phenyl substituent on the alkyne were not selective in the 5-*exo-dig* pathway with NHC ligand IPr **(L9)**. In the same way, two other substrates (**3.96c**) and (**3.96g**) with a methyl substituent on the alkyne was not selective in the 6-*endo-dig* pathway with the bulky biphenylphosphine Me_4tBuXPhos **(L8a)**.

One of the key concepts to control the *5-exo-dig* vs *6-endo-dig* pathway is the polarization of the alkyne.**Error! Bookmark not defined.** We decided to investigate if electronic biases would have a big impact on our systems with respect to the *5-exo*/*6-endo* selectivity and if we could overcome it by the use of specific ligands. We explored the cyclization of para-substitued aryl groups on alkyne substrates **(3.96)** using *exo*-selective condition with ligand IPr (**L9**), using *endo*-selective conditions with ligand Me_4tBuXPhos **(L8a)** and using ligand JohnPhos (**L1a**) as a standard (**Table 3.06**). When a methoxy (**OMe**) substituted substrate (**3.96j**) was subjected to the catalyst armed with the NHC ligand IPr (**L9**), a poor ratio of 24:76 disfavoring *5-exo-dig* product (**3.98j**) was obtained (**entry 1**). On the other hand, 6-*endo-dig* product (**3.99j**) could easily be furnished from (**3.96j**) with exclusive selectivity when Me_4tBuXPhos (**L8a**) and JohnPhos (**L1a**) was used as ligands. Replacing group **X** for a methyl (**Me**) substituent still made the *5-exo-dig* cyclization of **(3.96k)** difficult, furnishing compound **(3.98k)** as the minor product in a 46:54 ratio with NHC ligand (**L9**) (**entry 2**). Cyclization of **(3.96k**) using both biphenylphosphine catalysts afforded excellent selectivity for the 6-*endo-dig*-carbocyclization and furnished bicyclic compound **(3.99k)** in 89% and 78% yield with JohnPhos (**L1a**) and Me_4tBuXPhos (**L8a**) ligands respectively. When a weak electron-withdrawing group (EWG) such as a methyl ketone (**COMe**) was used, we were able to obtain a 84:16 ratio favoring **(3.98l)** using NHC ligand IPr (**L9**) and a reverse ratio of 29:71, favoring **(3.99l**), using bulky ligand Me_4tBuXPhos (**L8a**) (**entry 4**).



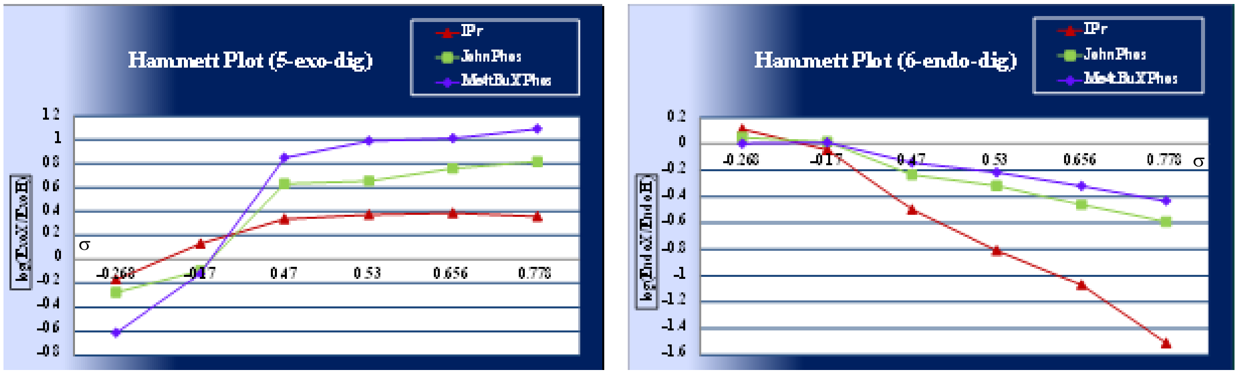
entry	substrate	X	L = IPr (L9) yield (ratio)	L = JonhPhos (L1a) yield (ratio)	L= Me4tBuXPhos (L8a) yield (ratio)
1	3.96j	OMe	90% (26:74)	93% (≤ 05:95)	75% (≤ 05:95)
2	3.96k	Me	93% (46:54)	89% (08:92)	78% (≤ 05:95)
3	3.96b	H	86% (40:60)	88% (10 :90)	77% (≤ 05 :95)
4	3.96l	COMe	91% (84:16)	84% (45:55)	75% (29:71)
5	3.96m	CF_3	89% (89:13)	76% (51:49)	75% (40:60)
6	3.96n	CN	88% (89:11)	84% (65:35)	67% (47:53)
7	3.96o	NO_2	80% (90:10)	78% (74:26)	65% (58:42)

Table 3.06 *Hammet study for IPr, JohnPhos and* Me_4*tBuXPhos ligands*

JohnPhos ligand (**L1a**) favors slightly the 6-*endo-dig* product (**3.99l**) in ratio of 45:55. When the cyclization was performed with a stronger electron withdrawing group like trifluromethyl- (**CF_3**), cyano- (**CN**) or nitro- (**NO_2**) **(3.96m, n, o)** and using σ-donating ligand IPr **(L9)**, 5-*exo-dig* products **(3.98m, n, o)** were all obtained with good selectivity and yield (**entries 5, 6** and **7**). However, progressive erosion of 6-*endo-dig* selectivity was observed for the corresponding decalins (**3.99m, n, o**) when silyl enol ethers (**3.96m, n, o**) were submitted to Me_4tBuXPhosAu(I) (**L8aAu+).** Compounds **(3.99m, n)** were obtained as the major products, albeit in moderate yields and poor *exo*: *endo* ratios (**entries 5** and **6**). Only decalin (**3.99o**) was obtained as the minor product. These results are more impressive when compared with results obtained using the JohnPhos ligand (**L1a**), where the *5-exo-dig* product (**3.98m, n, o**) was the major product for all these cases.

Our investigation on alkyne polarization brings us to examine the Hammett equation to probe the transition states of the 5-*exo-dig* and 6-*endo-dig* pathways. At first glance, these two competitive transition states demonstrated different behavior but all the ρ values are comprising between -1≥ 0 ≤ 1, meaning a weak susceptibility of this reaction to the electronic parameter.

The difference in the sign of the slope for the 5-*exo-dig* and the 6-*endo-dig* is characteristic of both transition states. It is important to note that the protodeauration can be the rate-determining step. However, the transition state of the first carbon-carbon bond formation fit well to explain the behavior of these Hammett plots. The positive slope in the case of the 5-*exo-dig* pathway could arise from the electronic flow towards the aromatic ring during the slippage of the gold(I) complex to the carbon 1 of the alkyne. In the case of the 6-*endo-dig* pathway, during the slippage of the gold(I) complex towards the carbon 2 of the alkyne, the electrons flow away from the aromatic ring, explaining the negative slope. The sudden change in slope for the 5-*exo-dig* pathway should mean a change in the mechanism and maybe a change in the position of the transition state. With strong electron-donating group, their ability to stabilize cationic charge could bring the transition state later in the reaction coordinate.



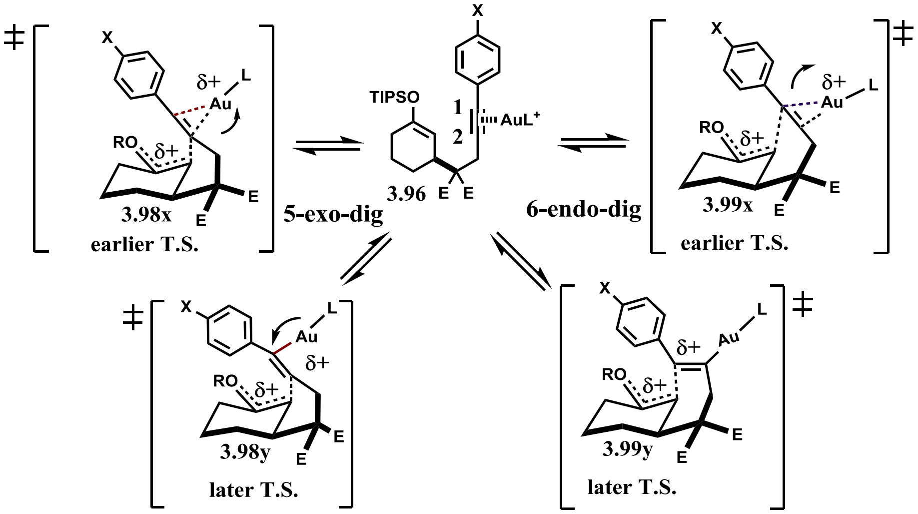
IPr	JohnPhos	Me$_4$tBuXPhos
$y1 = 0.25\rho - 0.41$	$y1 = 0.46\rho - 0.82$	$y1 = 0.73\rho - 1.43$
R2 = 0.99	R2 = 0.90	R2 = 0.97
$y2 = 0.02\rho + 0.31$	$y2 = 0.07\rho + 0.55$	$y2 = 0.07\rho + 0.80$
R2 = 0.94	R2 = 0.95	R2 = 0.92

IPr	JohnPhos	Me$_4$tBuXPhos
$y = -0.35\rho + 0.27$	$y = -0.15\rho + 0.11$	$y = -0.10\rho + 0.10$
R2 = 0.99	R2 = 0.97	R2 = 0.99

$y = \sigma\rho$

Figure 3.07 *Hammett plot for 5-exo-dig and 6-endo-dig carbocyclizatuon with IPr, Me$_4$tBuXPhos and JohnPhos ligands*

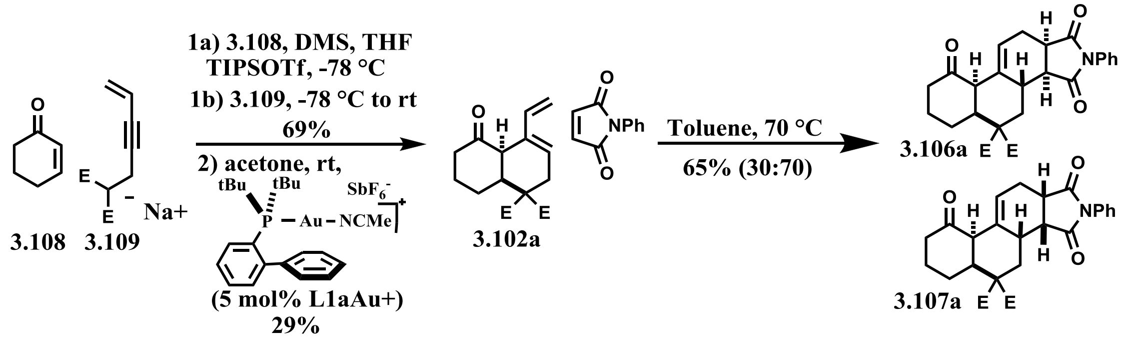
The more positive slope could represent the largest increase in the migration of the gold(I) complex toward carbon 1 next to the aromatic ring. On the other hand, a sudden change in the slope should indicate a change in the rate-determining step. With electron-donating groups, the rate-determining step could be the carbon-carbon bond formation; while with electron-withdrawing groups protodeauration could be the rate-limiting step, explaining the weak susceptibility of this reaction to the electronic parameter. The quasi-neutral slope with electron-withdrawing groups could also be attributed to the electronic stabilization brought by these gold(I)-complexes during the transistion state. In fact, the gold(I)-complex with the σ-donating ligand IPr (**L9Au+**) is almost insensitive to the electronic perturbation (ρ = 0.02) in the 5-*exo-dig* pathway. In the case of the 6-*endo-dig* pathway, the later transition state of the NHC gold(I) complex (**L9Au+**) associated with the development of partial positive charge could explain the more negative slope exhibited by this complex. For this pathway, the gold(I) complex embedded with the bulky biphenylphosphine Me$_4$tBuXPhos ligand (**L8aAu+)** is the less sensitive towards electronic perturbation.



Scheme 3.13 *Possible transition states for the 5-exo-dig and the 6-endo-dig*

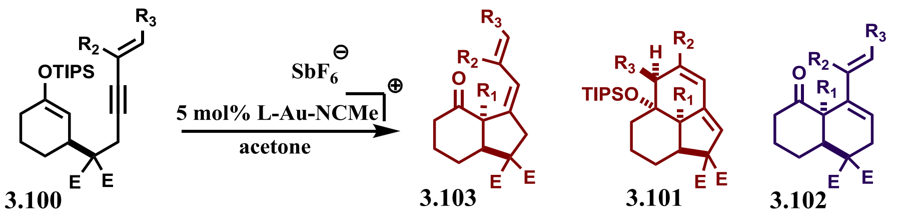
3.10 Scope of the selective gold(I)-catalyzed synthesis of fused carbocycles: vinyl substituents

With the demonstration that the ancillary ligand can influence the regioselectivity of the carbocyclization, this opened up new possibilities in terms of diene syntheses. We rapidly came back to vinyl-containing substituents in order to get better selectivity for the desired diene (**3.102**). If we can selectively access the 6-*endo-dig* pathway on this system, we could enable a quick synthesis of diterpene and steroid frameworks since the desired polycyclic structures are obtained through a subsequent Diels-Alder reaction. In collaboration with master student Patrick Levesque, we first confirmed the feasibility of the Diels-Alder reaction and obtained polycycles (**3.106a**) and (**3.107a**) in 65% yield with diasteroisomeric ratio of 30:70.[42] Inspired by the synthetic potential of this sequence and in order to improve its modularity, we explored the scope of the vinyl substituent (**Table 3.07***)*. A quick overview shows that the 6-*endo-dig* pathway is more challenging with these type of substrates and no product bearing a quaternary angular methyl at the ring junction was obtained.



Scheme 3.14 *Three step synthesis of polyclic framework related to steroid from cyclohexenone*

The 5-*exo-dig* pathway leads to the formal [4+2] product except when **R3** is substituted. To our delight, substitution on **R2** and/or **R3** is well tolerated in the 6-*endo-dig* cyclization. On the unsubstituted enyne (**3.100a**), ligand Me$_4$tBuXPhos (**L8a**) helped us to obtain an increase of 10% yield of the desired diene (**3.102a**) compared to JohnPhos **(L1a)**, but always as the minor product (**entry 2**). We then looked at varying vinyl substitution and discovered that when **R2** is methyl (**Me**), the formal [3+2] cycloadditon is also possible, leading to a mixture of three different products (**entries 3-4**). However, it appears that the electronic stabilization brings by this vinylic group allows the *6-endo-dig*/Prins cyclization cascade to furnish tricyclic compound (**3.104c**) in small quantities. After purification, the tricycle (**3.101c**) can be isolated in 54% yield with the NHC ligand IPr (**L9**) and using bulky ligand Me$_4$tBuXPho**s (L8a)**, the desired diene (**3.102c**) can be isolated in 65% yield. To our delight, when methyl (**Me**) substitution is present at both positions on the alkene the desired diene can be isolated in high yield, 86% (**entry 5**). Selective synthesis of both bicycle (**3.103g**) and tricycle (**3.102g**) provides another beautiful example of the impact of the ligand on the modulation of the pathway (**entries 6** and **7**). Finally, substitution on the internal position of the vinylic position (**R2**) slows down the cyclization, but good selectivity and moderate yield for the desired dienes (**3.102h-i**) can be obtained. Substrate (**3.100i**) needs tBuXPhos (**L3a**) as a ligand for moderate conversion and only the desired bicycle (**3.102i**) was isolated in moderate 48% yield (**entry 9**).



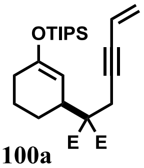
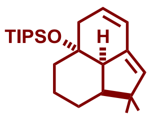
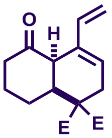
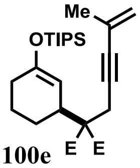
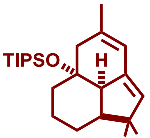
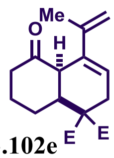
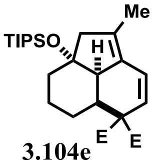
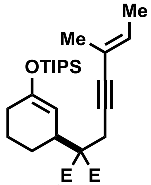
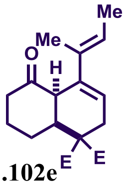
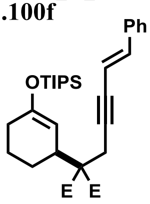
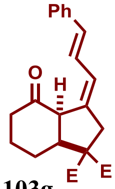
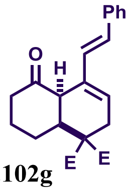
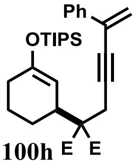
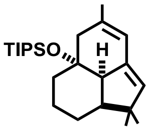
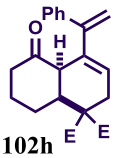
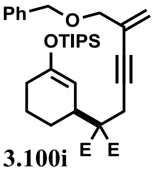
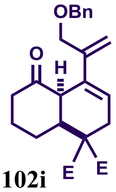
entry	substrate	ligand(condition)	product	yield (ratio)
1	 3.100a	JohnPhos, acetone, rt	 3.101a  3.102a	83% (100 :00)
2		Me$_4$XPhos, acetone/MeOH, rt		98% (58:42)
3	 3.100e	IPr, MeOH, rt	 3.101e  3.102e  3.104e	77% (68:18:14)
4		XPhos, MeOH, rt		86% (17:76:11)
5	 3.100f	Me$_4$XPhos, acetone, rt	 3.102e	86%
6	 3.100g	IPr, acetone, rt	 3.103g  3.102g	97% (97:03)
7		Me$_4$XPhos, acetone, rt		84% (13:87)
8	 3.100h	Me$_4$XPhos, acetone, rt	 3.101h  3.102h	71% (15:85)
9	 3.100i	tBuXPhos, acetone, rt	 3.102i	48%

Table 3.07 *Scope of the vinyl substituent in the gold-catalyzed 6-endo-dig carbocyclization*

3.11 Brief explanation of the ligand impact on the regioselectivity of the selective gold(I)-catalyzed synthesis of fused carbocycles

This ligand's impact on the regioselectivity of the gold(I)-catalyzed carbocyclization is quite hard to explain. In **Section 3.4**, we have seeing the electronic properties that the ligand JohnPhos (**L1a**) and IPr (**L9**) imparts to their corresponding gold(I) complex and how these ligands influence the reactivity of those complexes in cycloisomerization of 1,6 enynes. In these cases studied, the reaction pathway bifurcation point was obtained when the gold was covalently bonded to the substrate and the electronic properties of those ligands can directly influence the capacity of the catalyst to stabilize cationic intemediates. However, to the best of our knowledge this study show for the first time that the ancillary ligand can influence the pathway leading to selectivity through the first bond formation rather than through a common intermediate generated after an initial bond formation. One of our first observations was the relation between the angle of the phosphine-gold-chloride bond of the related gold(I) catalyst and the formation of the 6-*endo-dig* product (**3.96f**). Our catalyst which was found to be the most selective towards this end, Me_4tBuXPhosAu(I) complex (**L8aAu+),** had the most acute angle in all complexes studied (**Table 3.08**). The weak arene interaction with the gold atom and the biphenyl moiety induces a unique steric environment and as a consequence, distorts the linear geometry around the gold atom. As both ligands on the gold atom are in competition for the electronic density, distortion in the geometry suggests that, in at least one gold-ligand couple, the orbital overlap with full d orbital of the gold(I) metal is reduced. Toste proposed that π-donation from gold to carbon is actually reduced. This hypothesis explains the more cationic pathway often followed by the biphenylphosphine ligand, but in the case of Toste's example, JohnPhos (**L1a**) and IPr (**L9**) gives the same selectivity, in opposition to the selectivity obtained with the phosphite ligand.[42] These inconsistencies underlie the complexity of understanding the ligand's impact in gold catalysis. However, our studies suggest that this angle (phosphine-gold-ligand) could have an important impact in the selectivity of gold(I) catalysis. The NHC IPr ligand (**L9**) possesses bulky substituents, but since the arenes are far away from the gold center, the complex geometry is perfectly linear. This ligand has a strong σ-donor property and weak π-acidity. The π-donation of the gold to the cationic intermediate should be high and this ligand provides the most selective catalyst towards the 5-*exo-dig* carbocyclization of silyl enol ether (**3.96f**), while often only trace amounts of the secondary product was detected.

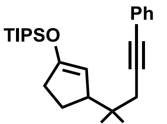
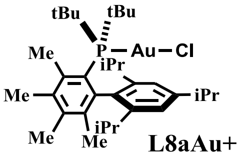
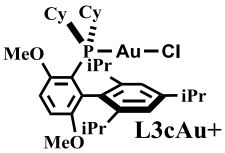
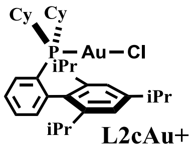
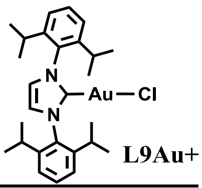
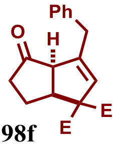
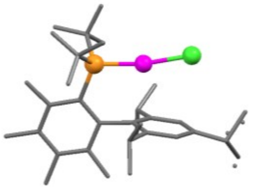
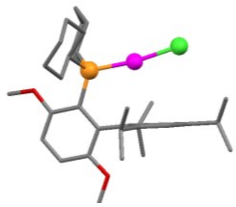
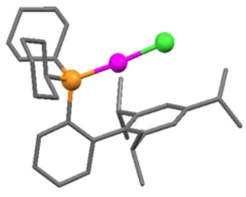
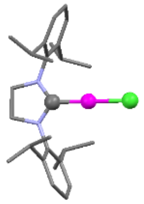
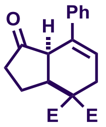
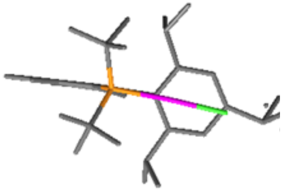
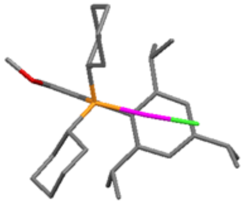
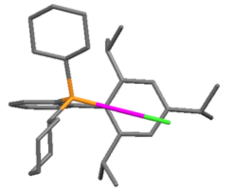
 3.96f	 L8aAu+	 L3cAu+	 L2cAu+	 L9Au+
ligand	**Me$_4$tBuXPhosAuCl**	**BrettPhosAuCl**	**XPhosAuCl**	**IPrAuCl**
angle P-Au-Cl	**169.23°**	**171.38°**	**176.68°**	**180.00°**
ratio endo/exo substrat 3.96f	**29 : 71**	**38 : 62**	**67 : 33**	**95 : 05**
 3.98f				
 3.99f				

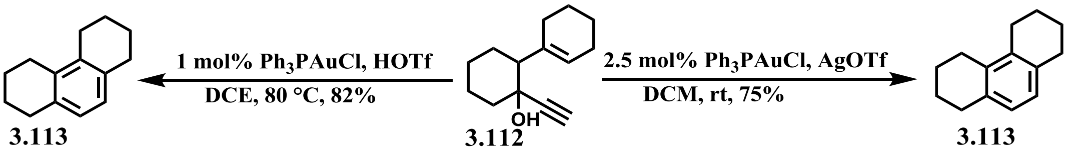
Table 3.08 *Angle variation of gold(I) complex and its impact on the regioselectivity of the gold(I)-catalyzed carbocyclization*

With the XPhos ligand (**L2c**), the major pathway is still the 5-*exo-dig* cyclization, but the biphenyl moiety slightly distorts the gold geometry and the angle between the phosphine-gold-chloride is 176.68°. The complex with the ligand BrettPhos (**L3c**) favors the 6-*endo-dig* pathway and we can observe that the distortion is still increasing in the neutral gold(I) complex with an obtuse angle of 171.38° The addition of rigidity brought by the three iso-propyl moieties on the right-most phenyl and the two methoxy substituents on the left-most phenyl forces this distortion in order to release some steric strain . This effect was found to be maximum for the ligand Me$_4$tBuXPhos **(L8a)**, where the four methyl groups on the left ring rigidify the phosphine geometry by pressuring the gold center towards the shielding 2,4,6-triisopropylphenyl group and thereby increasing the steric crowding of the metal center. We can observe this effect with crystallographic data analysis and find that the gold-chloride bond is perfectly aligned with the second phenyl. To the best of our knowledge this mono-metallic gold(I) complex has one of the biggest distortion of the linear geometry reported to date. As we have seen, this complex brings unique reactivity and affords good selectivity for the 6-*endo-dig* pathway. Moreover, recent work in the Zhang group also reports the unique reactivity of this gold complex (**L8aAu+**).[44]

Indeed, they have calculated the percent buried volume value defined as the percent of the total volume of a sphere occupied by a ligand. This concept was introduced by Nolan and they found that Me$_4$tBuXPhos (**L8a**) has a higher %VBur value than any of the gold ligands investigated by Nolan.[45] This is not a definitive and quantitative explanation of the inversion of the regioselectivity but a useful guideline for the discovery of new catalysts with unique properties.

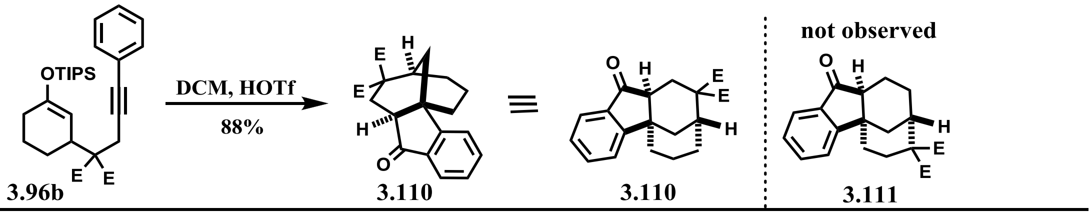
3.12 An intriguing triflic acid-mediated bond-forming-bond breaking cascade

During her research in gold(I) catalysis, Ph. D. student Christiane Grise-Bard found that gold(I) chloride complex can efficiently be activated to the cationic form by triflic acid instead of traditional silver salt (**Scheme 3.15**). This activation has been demonstrated in the gold(I)-catalyzed benzannulation and furnishes a better chemical yield for the synthesis of tetrahydronaphtalenes (**3.113**) with a lower catalyst loading. However, higher temperature is need and should not be neglected in the performance of the catalyst system.



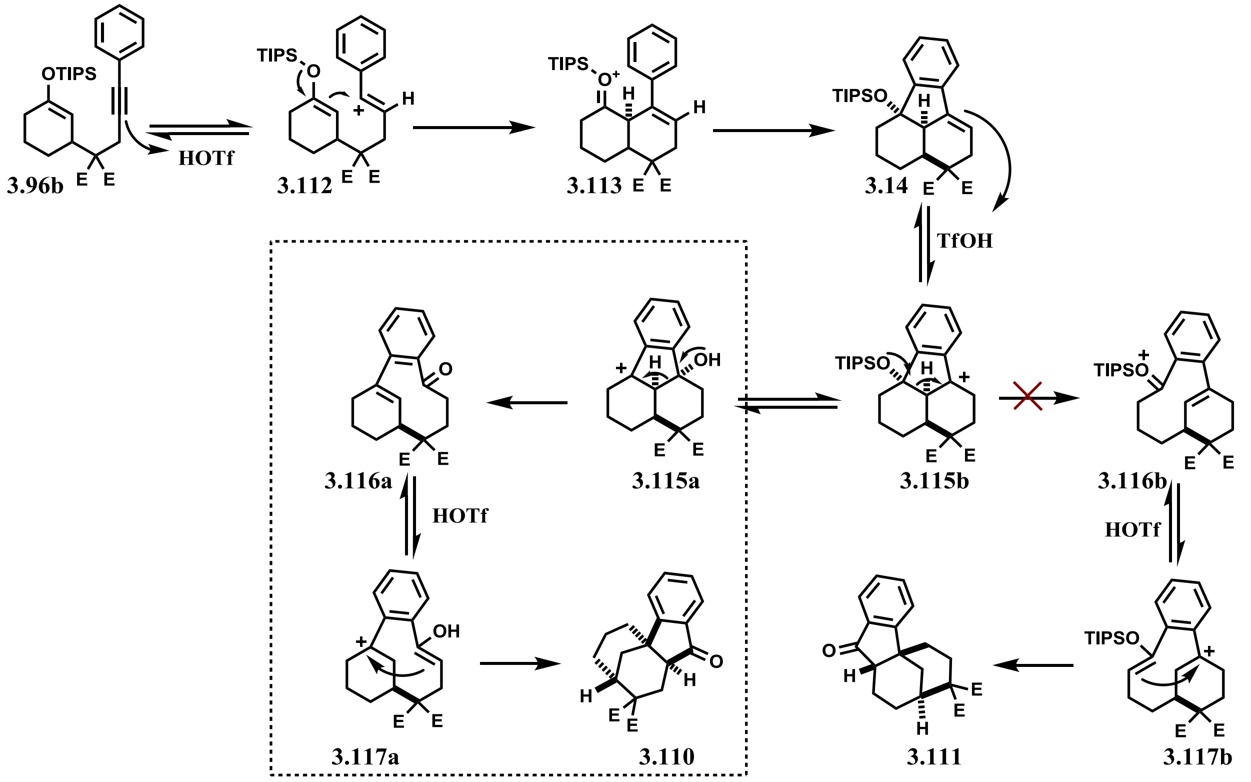
Scheme 3.15 *Activation of gold(I) chloride by silver salt and trifilc acid*

When this mode of activation was attempted on our system, an interesting tetracyclic structure (**3.110**) was isolated in good yield. Further exploration shows that a gold(I) catalyst was not necessary to the process (**Scheme 3.15**). We proposed a formal mechanism to explain the selective formation of the complex tetracyclic product (**3.110**) that can be isolated in 88% yield, over the formation of isomeric product (**3.111**).



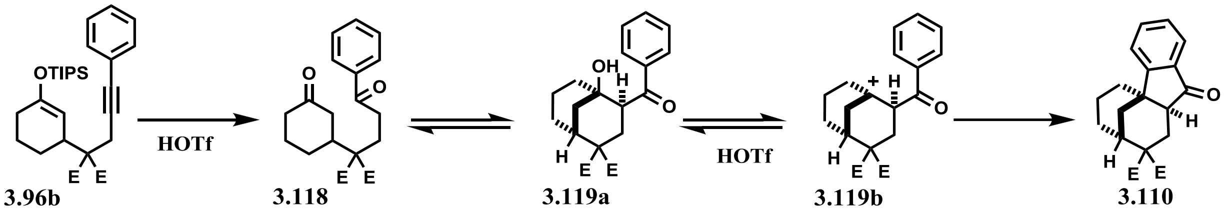
Scheme 3.16 *Discovery of the selective triflic acid mediated bond forming/ bond breaking cascade*

Protonation of the phenylalkyne (**3.96b**) by strong triflic acid produces benzylic carbocation (**3.112**), which can be trapped by an intramolecular cyclization of the silyl enol ether. The phenyl moiety can undergo an intramolecular Friedel-Craft type addition on the oxocarbenium (**3.113**) leading to tetracycle (**3.114**). Triflic acid is strong enough to protonate an alkene and to form the benzylic carbocation (**3.115b**). This intermediate will not undergo a Grob's-type fragmentation, but equilibrium between the two tertiary carbocations (**3.115b**) and (**3.1115a**) will take place. Thus, intermediate (**3.115a**) will be the carbocation that will undergo the Grob-type fragmentation to afford nine member rings (**3.116a**). Triflic acid will again protonate the cyclic alkene and generate the third benzylic carbocation (**3.117a**) in the mechanism. Carbocation (**3.117a**) can cyclize via its enol tautomer to finally provide the desired product (**3.110**). The equilibrium between carbocation (**3.115a**) and (**3.115b)** is not surprising under strong Bronsted acid condition such as triflic acid, but the origin of the selectivity during the mechanism is hard to explain. These two cationic intermediates (**3.115a**) and (**3.115b**) are quasi-symmetric; the only difference is the presence of a gem-dimalonate on one ring. This neighboring group could be responsible for the selectivity observed, but any rational had convinced us for the explanation of the selectivity observed.



Scheme 3.17 *Formal mechanism for the selective triflic acid mediated bond forming/ bond breaking cascade*

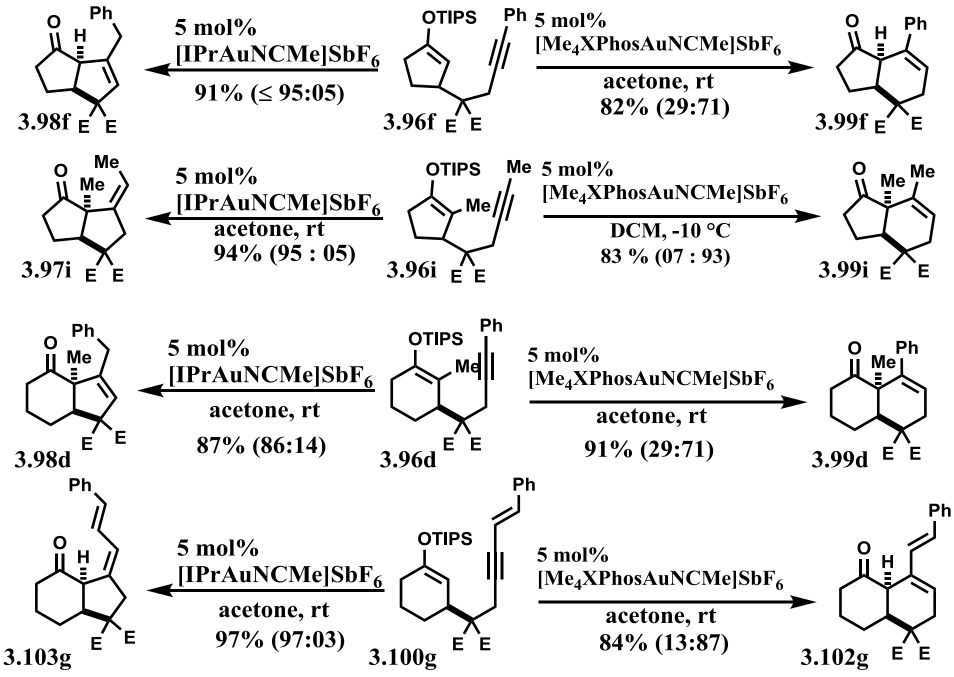
On the other hand, one can postulate that triflic acid and some moisture in the flask could hydrolyse the silyl enol ether (**3.96**) and hydrate the alkyne to the benzylic ketone (**3.118**). An intramolecular aldol reaction could construct the first carbon-carbon bond and generates the tertiary alcohol (**3.119a**). Triflic acid is enough strong to generate the carbocation (**3.119b**) and a subsequent Fridel-Crafts alkylation will form the second carbon-carbon bond. While this formal mechanism explains the selective formation of polycyclic (**3.110**) over (**3.111**), the Fridel-Crafts alkylation of a non-planar carbocation and an electron poor aryl seems a highly energetic process.



Scheme 3.18 *Formal mechanism for the selective triflic acid mediated bond forming/ bond breaking cascade*

3.13 Highlight and limitation of the gold(I)-catalyzed synthesis of fused carbocycles

In summary, we have demonstrated that the gold(I)-catalyzed 6-*endo dig* pathway is accessible and not limited to substrates possessing steric, electronic or stereoelectronic biases. Even substrates with strong electron withdrawing groups that disfavor the polarity of the alkyne were prone to follow this pathway. The ancillary ligand can effectively influence the pathway selectivity for the first bond formation rather than through a common intermediate generated after an initial bond formation. Our desire to favor the 6-*endo-dig* pathway in the gold(I)-catalyzed carbocyclization allow us to recognize that Me_4tBuXPhosgold(I) complex (**L8aAu+)** can be uniquely effective and selective in gold(I)-catalyzed reactions. The strongly hindered environment that this ligand brings to the gold(I) center enables unique reactivity and selectivity. Our investigation led to another beautiful example of the diagonal reactivity that NHC carbene and biphenyl phosphine ligands could bring to gold(I) catalysis. This study finally concludes on a selective gold-catalyzed divergent synthesis of fused carbocycles via a regioselective *6-endo-dig* or *5-exo-dig* carbocyclization. Four selected examples highlight the control that can bring gold(I)-catalysis to these mechanistic pathways (**Scheme 3.19**).



Scheme 3.19 *Summary of the divergent synthesis of fused carbocycles via a selective 5-exo-dig or 6-endo-dig carbocyclization*

These four examples resume the generality of our method where 5 and 6 member rings templates are present, as phenyl, methyl and vinyl substitution on the alkyne and also the formation of an vicinal quaternary center. Good to excellent selectivity was achieved in both the *5-exo-dig* and the *6-endo-dig* carbocyclization pathways. Furthermore, this type of transformation could provide an access to synthetically useful carbocyclic motifs that are found in numerous diterpenoid natural products. The applications of these catalytic processes to the synthesis of natural diterpenes frameworks will be reported in the following chapter.

It is also important to highlight the limitations encountered. Three examples are provided in each pathway where our two identified ligands bring no selectivity or slightly favor the opposite pathway. These substrates can be a more sensitive probe to further improve catalyst design and property. As a result of the high efficiency of ligand IPr (**L9**) and of the less attractive synthetic potential of the 5-*exo-dig* pathway, we did not perform as in depth investigation on NHC ligands than on biphenylphosphine ligands, but the same work can be done in the future for the purpose of identifying other interesting ligands.

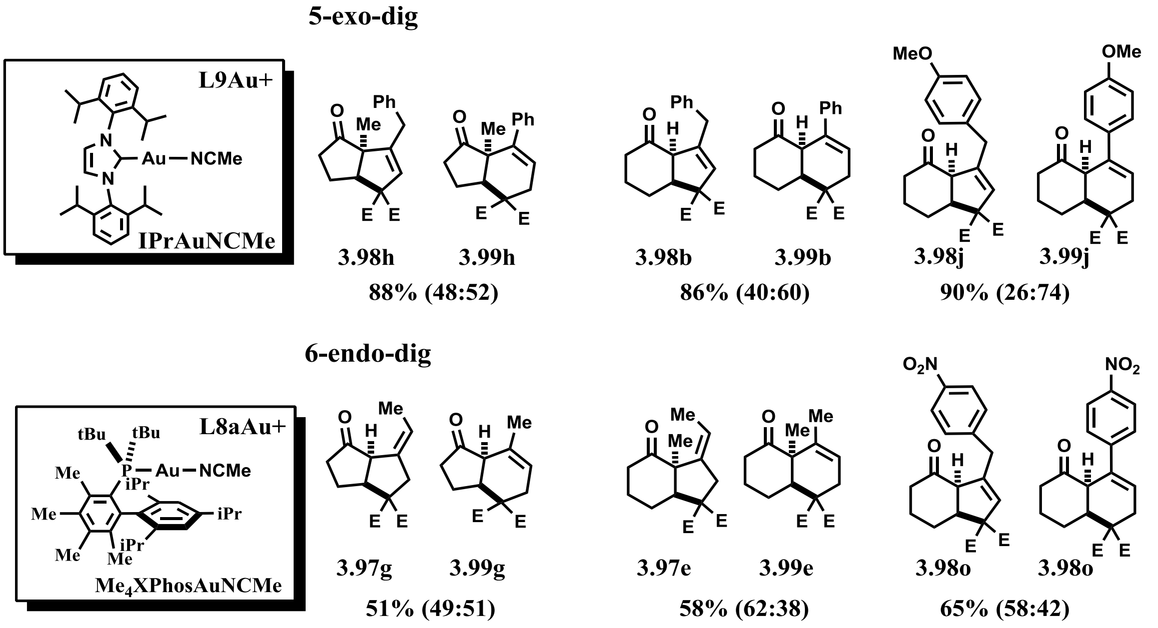


Table 3.09 *Summary of limitations observed for both ligands IPr* **(L9)** *and Me$_4$tBuXPhos* **(L8)**

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Chapter 4

Building Molecular Diversity by Gold(I)-Catalysis

4.1 Introduction to steroids: chemical structures and biological activities

Unfortunately today, the effects of anabolic steroids and their use in doping to enhance athletic performance led to their bad reputation. However, these polycyclic terpenoids traditionally play a vital role in the development of organic synthesis and the development of new medicines.[1] For example, of the top 200 drugs prescribed in 2011, twenty were steroid-based medicines.[2] Steroid based drugs have indications against a myriad of different diseases including asthma, cancer, arthritis, allergies and are also used as birth control.[3] The broad effectiveness of steroid drugs are due to their presence in various physiological processes, including stress response, immune response, inflammation regulation, carbohydrate metabolism, protein synthesis, blood electrolyte levels, membrane fluidity, and reproduction.[4] The isolation of the first steroid, cholesterol, was performed in 1769 and rediscover in 1815, but the correct chemical structure was not elucidated until 1932.[5] In 1939, Bachmann reported the first total synthesis of a natural steroid, equilenin.[6] Numerous groups including, Robinson, Fieser, Woodward, Barton, and Jones, were involved in the early chemical research aimed at the synthesis of steroids.[7]

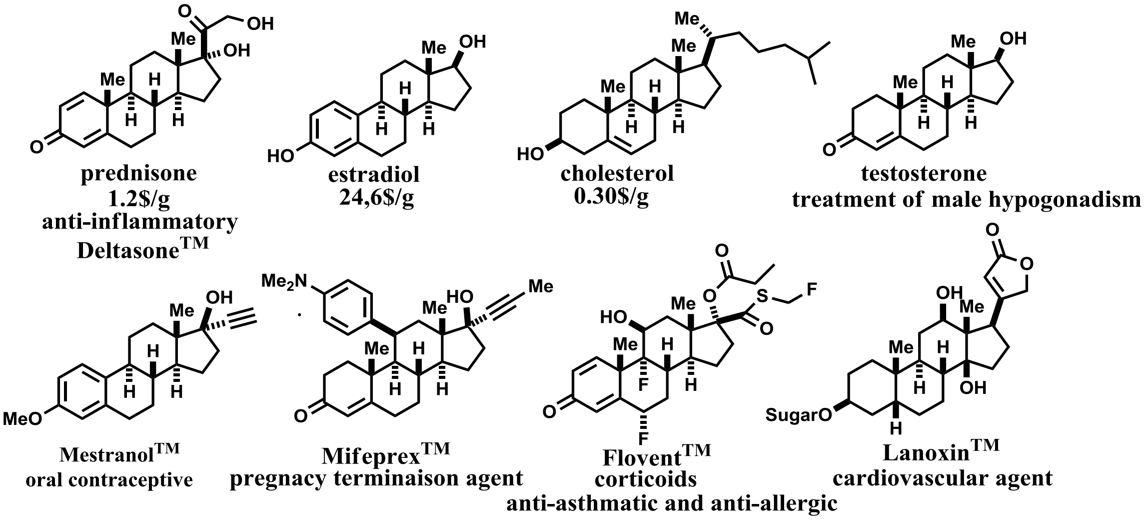
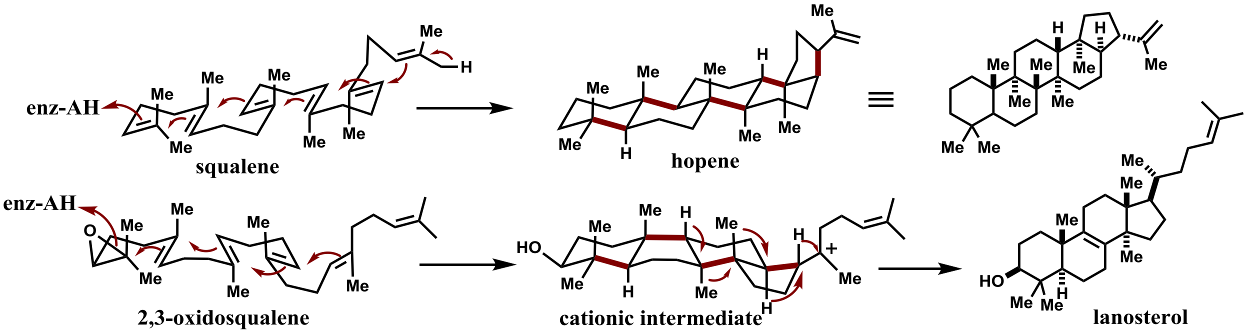


Figure 4.01 *Representative natural steroids and commercial steroid-based medicines*

Since the elucidation of the enzymatic cyclization mechanism of squalene and 2,3-oxidosqualene to form polycyclic triterpenes, chemists have been fascinated by the impressive efficiency of the nature to build diverse and complex molecules from simple components. In this specific case, polyolefins such as squalene or 2,3-oxidosqualene are stereoselectively cyclized and skeletally rearranged in a single enzyme-catalyzed reaction to yield tetracyclic and pentacyclique terpenoids such as hopene and lanosterol (**Scheme 4.01**).[8] These triterpenes serve as biosynthetic precursors to the other steroids, including cholesterol, estrogen, androgens, and progesterones. Cyclization is proposed to occur via a π-cationic cascade reaction triggered by enzyme-promoted protonation at the terminal olefin of squalene, or by protonation of the epoxide of 2,3-oxidosqualene. For the synthesis of the other members of the family, subsequent modification of the core and the side chain is performed by a distinct set of enzymes.[9]

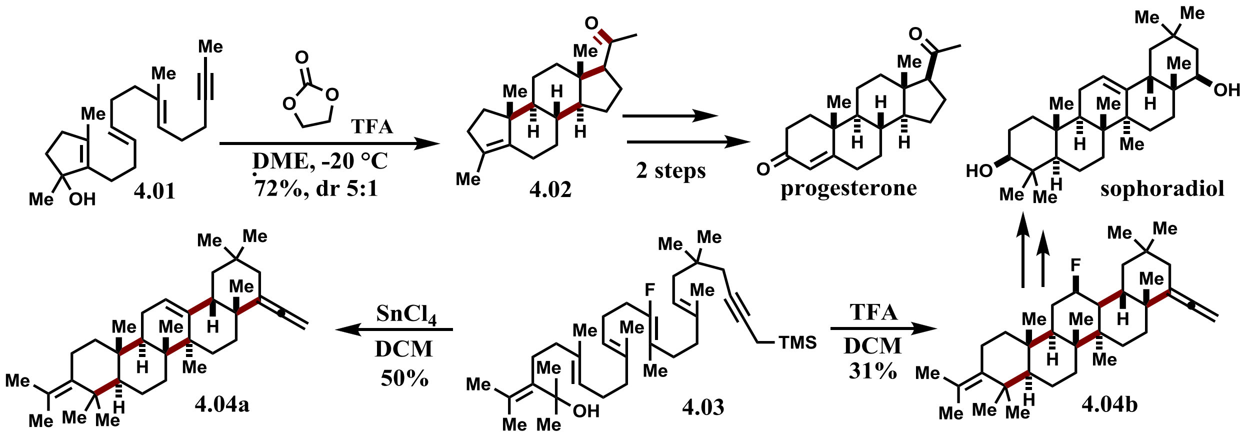


Scheme 4.01 *Biosynthesis of hopene and lanosterol from squalene.and 2,3-oxidosqualene*

Although few synthetic strategies for the preparation of polycyclic steroid related frameworks have been developed over the last decades, the synthesis of complex steroids and its pharmaceutical industrial preparation are generally based on the modification of inexpensive natural products (semisynthesis).[10] Currently, most steroid-based medicines are prepared by semisyntheses, including Deltasone (anti-inflammatory agent), Flovent (antiasthmatic and antiallergic agent), Lanoxin (cardiovascular agent), Mifeprex (pregnancy termination agent), Testosterone (treatment of male hypogonadism), and Mestranol (oral contraceptive) (**Figure 4.01**). This can be rationalized by 1) the difficulty to efficiently synthesize such complex polycyclic frameworks and 2) the abundance of naturally cheap sources such as cholesterol. The development of new synthetic transformations from simple linear precursors is the only competing alternative to efficiently synthesis their complex polycyclic frameworks. However, other than the biomimetic enzymatic polycyclization of olefins, only limited methods have been developed for the transformation of a simple linear substrate into a polycyclic steroid framework.[11] Moreover, these methods do not allow simple substrate modification which increases the complexity to synthesize various analogues via an unique strategy. This introduction will cover early research that led to two classical total syntheses of progesterone, recent developments in enanantioselective versions of the cationic polyolefin cyclization and approaches leading quickly to the steroid-related framework from linear precursors.

4.2 Classic steroids synthesis

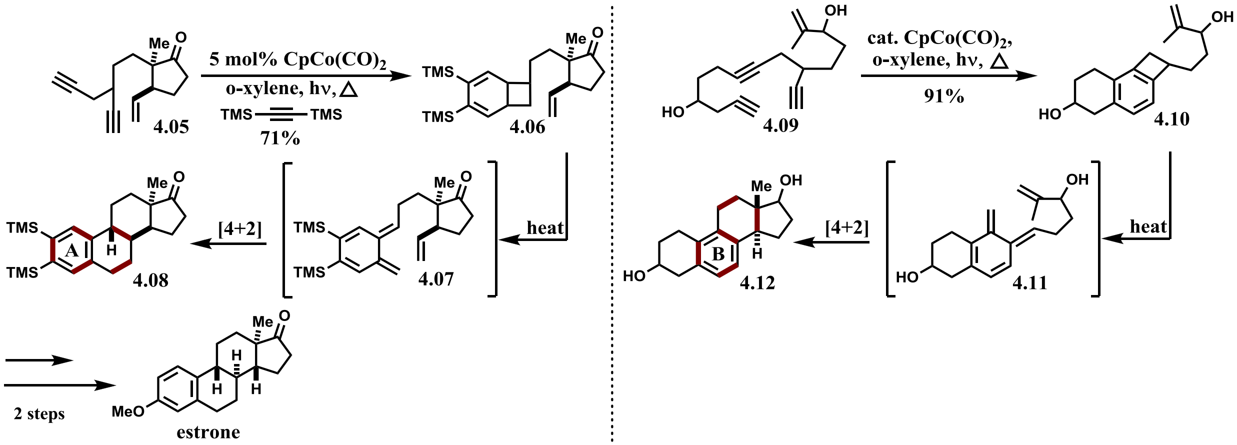
The pioneering work of Stork and Eschenmoser on the mechanistic stereochemical model for steroid biosynthesis and their related synthetic studies has created a solid foundation on polyolefin cyclization. This ground-breaking work ultimately led to the classical total synthesis of progesterone by Johnson (**Scheme 4.02**).[12] Van Tamelene, Corey, Overman and Nishizawa, have also contributed in this field.[13] To achieve this landmark, Johnson and colleagues have developed initiators and terminators in order to better control the polycyclization and to expand the scope of the cationic polyolefin cyclization. He exploited acetal functionality, and allylic alchohols as initiators and used alkynes, allyls, and propargyl silanes as terminators. In the early stage of his program directed towards the development of biomimitic cyclizations, he reported the synthesis of progesterone.[14] Treatment of polyolefin (**4.01**) with trifluoacetic acid and ethylene carbonate furnished tetracyclic compound (**4.02**) after a basic work-up. This intermediate can be further transformed into progesterone via ozonolysis and aldol condensation. Johnson and colleagues also reported that fluorine atom can serve as cationic stabilizing group to better control the regioselectivity in the biomimetic pentacyclization of polyene (**4.03**).[15]



Scheme 4.02 *Johnson's classic total synthesis of progesterone and first pentacyclization*

The Lewis acid $SnCl_4$ was effective for this process but resulted in an undesired dehydrofluorination product (**4.04a**) in a moderate 50% yield. Interestingly, Johnson's research group was able to perform the first biomimetic pentacyclization with trifluoroacetic acid to afford the pentacyclic product (**4.04b**) in 31% yield without elimination of HF. The pentacyclic intermediate (**4.04b**) was then converted into the triterpene natural product sophoradiol in three additional steps.[16]

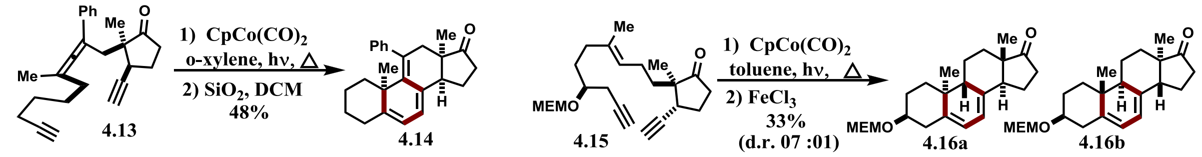
Another classic example, is the efficient synthesis of estrone realized by Vollhardt using a cobalt-mediated, cyclotrimerization/*o*-quinodimethane cycloaddition strategy (**Scheme 4.03**).[18] With this strategy, Vollhardt developed several syntheses of steroid skeletons where the aromatic ring formed can be the A, B or C ring.[19] The reaction was based on an intermolecular [2+2+2] cycloaddition, catalyzed by a cobalt(I) complex (**$CpCo(CO)_2$**), between a suitable di-yne (**4.05**) and bis(trimethylsilyl) acetylene to provide a benzo-cyclobutene (**4.06**). Under the reaction condition used, the formed benzocyclobutene (**4.06**) underwent conrotatory ring opening to give a highly reactive *o*-quinodimethane (**4.07**). Finally, the diene (**4.07**) reacted through an intramolecular Diels–Alder reaction with an unactivated olefin to afford the steroid skeleton (**4.08**) in an overall 71% yield. The total synthesis was finalized in two further steps via the selective functional transformation of bis-silane (**4.08**) to deliver the desired estrone. The design of triynene (**4.09**) and the use of cobalt complexes allowed the direct assembly of all four rings from a linear precursor to give the aromatic ring B derivative (**4.12**) having 100% *trans* stereochemistry at the ring junction.



Scheme 4.03 *Vollhardt classic total synthesis of estrone and steroid-related framework*

The cobalt-catalyzed cyclization of triynene **(4.09)** could be performed in one step or could be interrupted at the benzocyclobutene intermediate (**4.10**). The heating of the latter compound furnished the Diels-Alder adduct (**4.12**). The basic steroid framework was thus constructed from a simple linear starting material in an impressive reaction cascade.

The cobalt(II)-catalyzed [2+2+2] cycloaddition strategy was later used by two other groups, Malacria and Groth (**Scheme 4.04**).[20] The intramolecular [2+2+2] cycloadditions of suitable substituted allenediynes (**4.13**) mediated by a cobalt(I) complex enable the synthesis of 11β-aryl steroid (**4.14**). A similar approach was also chosen by Groth for the synthesis of the basic skeleton of lumisterol-type steroids. Instead of an allene, a simple olefin with two alkynes was used in the [2+2+2] cycloaddition of substrate (**4.15**). After decomplexation with iron(III) chloride, a diastereoisomeric ratio of 7:1 favouring the desired isomer (**4.16a**) was obtained.[20b, c]

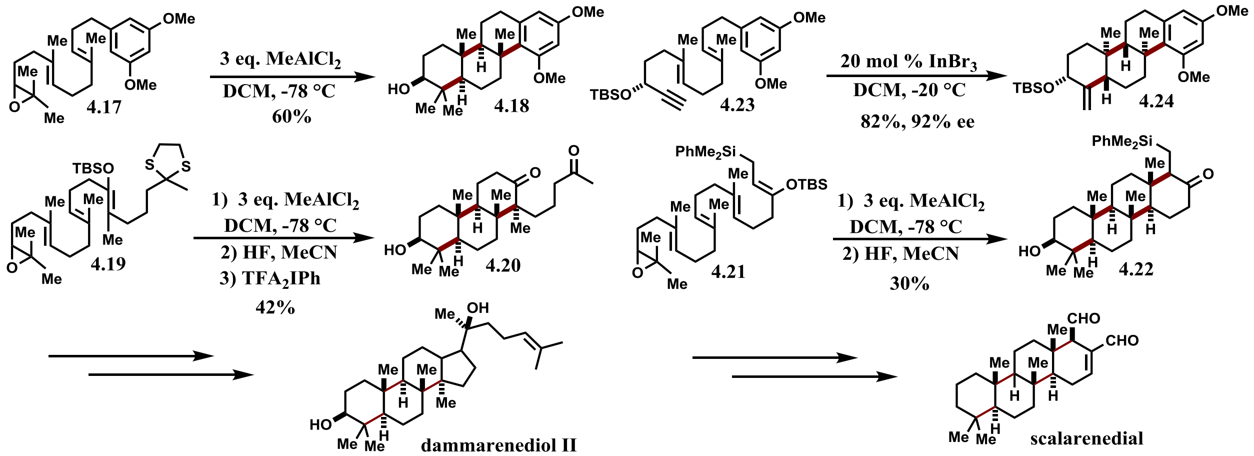


Malacria's Co(II)-catalyzed synthesis of 11β-aryl steroid skeletons **Groth's Co(II)-catalyzed synthesis of lumisterin precursor**

Scheme 4.04 *Cobalt(II)-catalyzed [2+2+2] cycloaddition in steroid-related framework synthesis*

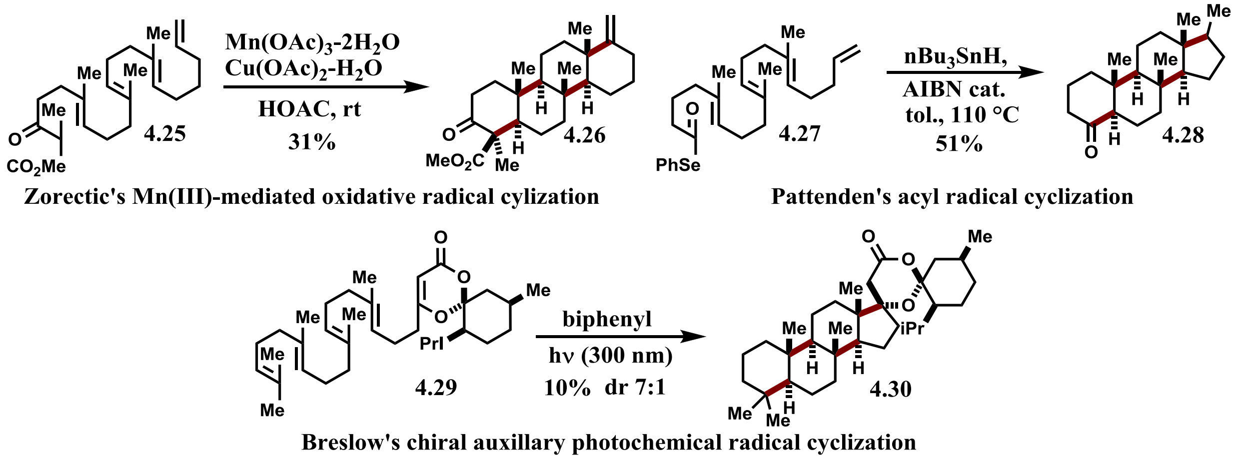
4.3 Precedent in the synthesis of steroids-related scaffold from linear precursors

The group of Corey utilizes the polyolefin cyclization strategy to prepare natural steroids (**Scheme 4.05**).[21] They used predominantly the interaction of an epoxide with an aluminum Lewis acid complex ($MeAlCl_2$) to initiate the polycyclization. For substrate (**4.17**), an aromatic ring was used as a terminator and the tetracyclic compound (**4.18**) was isolated in 60% yield. This successful approach was employed for the synthesis of, dammarenediol II and scalarenedial from silyl enol ether (**4.19**) and (**4.21**) respectively. It was found that the incorporation of enol ether allows for a better control of the final regioselectivity of tricyclic compound (**4.20**) and tetracyclic compound (**4.22**).[21d,g] Recently, the same group reported an indium(III)-catalyzed polyene cyclization of chiral propargylic silyl ethers to polycyclic products (**4.24**) in excellent yields and with high stereoselectivity.[22] Upon complexation with the triple bond, the soft Lewis π-acid initiated the polycyclization via an initial 6-*exo-dig* cyclization of enyne (**4.23**).



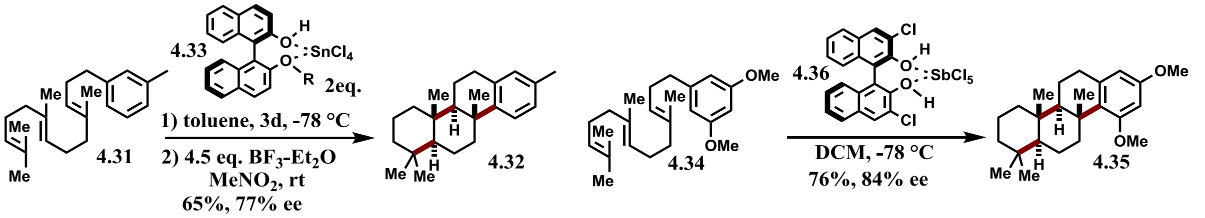
Scheme 4.05 *Selected examples of Corey's work in polyolefin cyclization*

Most of the early polyolefin cyclizations were based on the propagation of a cationic charge, but radical processes have also been exploited in the polyene cyclization (**Scheme 4.06**). In 1991, Zoretic was able to transform tetraene β-ketoester (**4.25**) to tetracycle (**4.26**) in 31% yield using manganese(III) based oxidative radical cyclizations.[24] Radical polycyclization is not limited to radical cation intermediates. Pattenden used an acyl radical generated from an acyl selenide (**4.27**) and Bu_3SnH-AIBN to achieve a tetracyclization with a 51% isolated yield of the polycyclic ketone (**4.28**).[25] In 1962, Breslow developed a photochemical radical process based on a biosynthetic proposal. A photoinduced electron transfer initiating the polycyclization by the formation of a radical cation which underwent a tetracyclization and reduction event.[26] The resulting polycyclic ketal (**4.30**) was obtained in a disappointing yield of 10%, but fortunately only two diastereoisomers were isolated with a 7:1 ratio.



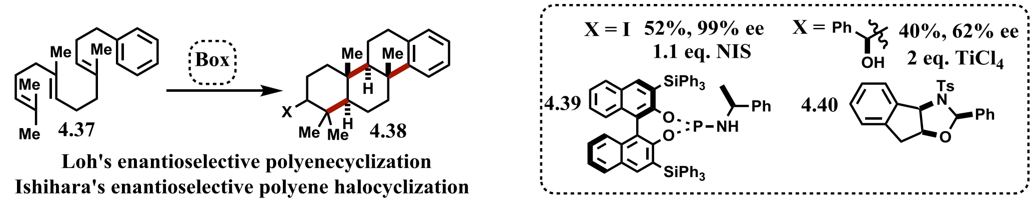
Scheme 4.06 *Radical-mediated polyolefin cyclization*

Recent development in asymmetric synthesis has enabled various strategies for the enantioselective biomimetic polyolefin cyclization (**Scheme 4.07**). The first example was reported in 1999 by Yamamoto and co-workers. [27] As an artificial cyclase, they developed a polycyclization reaction initiated by the selective protonation of terminal olefin, where a BINOL•$SnCl_4$ complex served as a chiral proton source. It was suggested that $SnCl_4$ and BINOL act as a Lewis acid assisted Brønsted acid (LBA), in which the native coordination simultaneously constrains the conformation of the BINOL O-H bonds and increases its acidity. In the presence of two equivalents of (*R*)-LBA **(4.33),** aryltriene (**4.31**) underwent polycyclization and subsequent treatment with BF_3-Et_2O affords tetracycle **(4.32)** with moderate yield and enantioselectivity. It should be noted that the first step of this sequence leads to a complex mixture and the use of an achiral Lewis acid in a second step provides the best results for maximizing the formation of tetracycle (**4.32**). In 2012, the group of Professor Corey improved this strategy with the use of a bulkier and stronger Lewis acid $SbCl_5$.[28] They also increased the acidity of the BINOL O-H bonds with the addition of chlorine in the *ortho* position. The reaction occurred rapidly at −78 °C and provided the polycyclic product with a better yield and higher enantioselectivity. In 2007, Ishihara reported the first synthetic method for the enantioselective halogen-induced π-cation cyclization of polyenes.[29] Treatment of aryltriene (**4.37**) with one equivalent of chiral *P*-iodophosphoramidite generated in situ with NIS and phosphoramidite (**4.39**) afforded the first cyclization. Subsequent exposure to $ClSO_3H$ delivered the desired polycyclic terpene **(4.38**) in 57% yield and 99% ee. A year later, Loh used an oxocarbenium intermediate as chiral promoter derived from *N*-acetal (**4.40**).



Yamamoto's first enantioselective polyene cyclization

Corey's enantioselective polyene cyclization

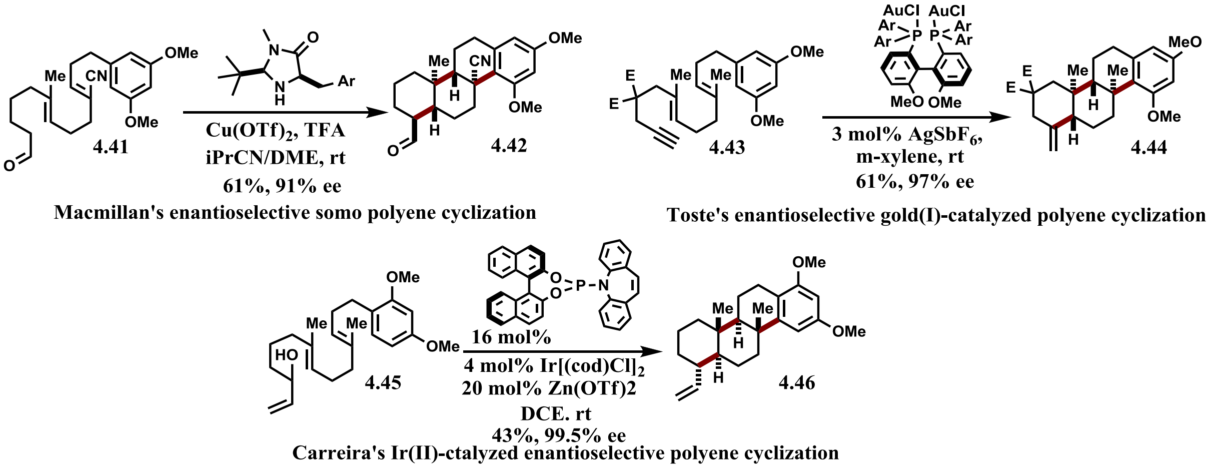


Loh's enantioselective polyenecyclization
Ishihara's enantioselective polyene halocyclization

Scheme 4.07 *Biomimetic enantioselective polyolefin cyclization*

Two equivalents of the titanium Lewis acid (**$TiCl_4$**) and of the chiral hemiaminal ether were necessary to achieve modest yield and enantioselectivity. [30] Although these approaches are innovative, early examples bring some limitations including the relatively small substrate scope, the requirement of stoichiometric chiral promoter, or the indirect access to polycyclic products.

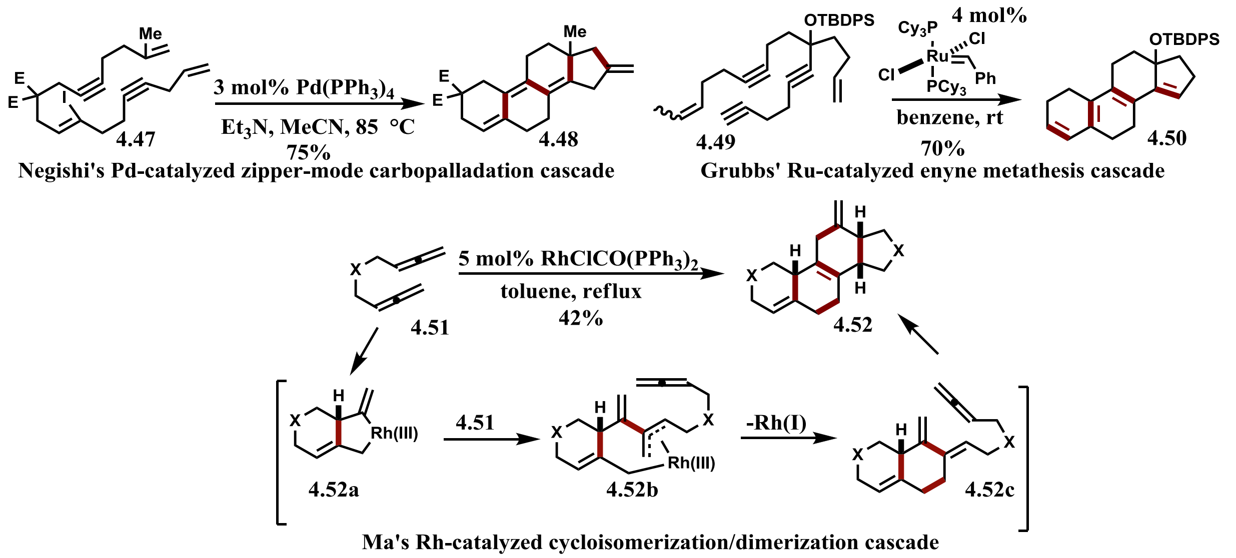
In 2010 MacMillan's group used its organo-SOMO-catalysis to develop the first catalytic enantioselective polyolefin cyclization via a single electron transfer cascade.[31] In order to avoid non-productive side reactions, they needed to alternate the polarity of the alkenes through the use of acrylonitrile and isobutylene moiety. The use of $Cu(OTf)_2$ as the oxidant in SOMO activation allows room temperature reactivity and affords the tetracyclic adduct (**4.42**) in a 61% yield and 91% ee. The first example of a highly enantioselective polyene cyclization reaction in which transition metal serves as the cyclization initiator was done in 2010 by Toste's group.[32] The (MeO-DTB-BIPHEP)gold(I)-catalyst initiated a 1,6-enyne cycloisomerization and subsequent polyolefin cyclization led to the tetracycle (**4.44**) in 61% yield and 97% ee. More recently, Carreira reported a highly enantioselective polycyclization method which was developed using the combination of Lewis acid activation and iridium-catalyzed allylic substitution.[33] Though the initial formation of an allyl-metal intermediate from polyene (**4.45**), tetracycle (**4.46**) was isolated in moderate yield, but high enantioselectivity.



Scheme 4.08 *Catalytic enantioselective polyolefin cyclization*

Except the polyolefin cyclization, only few synthetic methods have enabled the synthesis of polycyclic frameworks related to steroids from linear precursors.

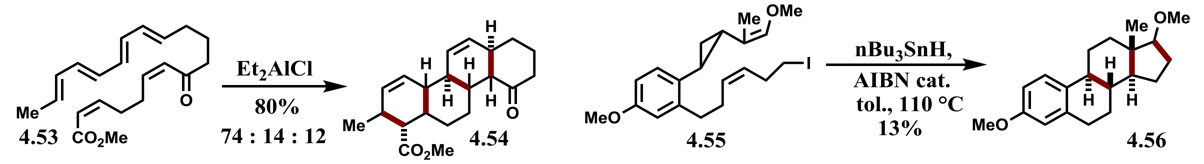
Through the judicious positioning of unsaturation within an acyclic precursor molecule, transition metal catalysis allows the selective formation of polycyclic steroid-type frameworks. (**Scheme 4.09**) In 1994, an elegant tetracyclization reaction involving the carbopalladation of an acyclic polyunsaturated precursor (**4.47**) was reported by Negishi.[34] The Pd(0)-catalyzed cyclization zipped the linear vinyl iodide precursor (**4.47**) and furnished tetracyclic (**4.48**) in 75% isolated yield. In 1998, Grubbs designed a polyenyne substrate (**4.49**) which selectively underwent three enyne methathesis and a ring closing methathesis in relay.[35]



Scheme 4.09 *Metal-catalyzed synthesis of polycyclic steroid-related scaffolds from simple linear precursors*

With 4 mol% of his first generation ruthenium catalyst, the polyenyne (**4.49**) triggered, at room temperature, a cascade sequence to afford the steroid-type compound (**4.50**) in 70% yield. The initiation of this highly selective process should occur with the insertion of the ruthenium alkylidene into the most kinetically reactive terminal alkene of polyenyne (**4.49**). The latter carbene species underwent enyne ring-closing metathesis with the proximal triple bonds until the terminating alkene ring-closing-metathesis event. Finally, in 2005 Ma demonstrated that by varying the rhodium precatalysts or the substitution of their bisallenes, different reactivity patterns could be observed.[36] When *trans*-rhodium complex ($RhCl(CO)(PPh_3)_2$) was used, selective dimerization occurs through an initial formation of a bicyclic rhodacyclopentane (**4.52a**), followed by the insertion of another allene. After reductive elimination of intermediate (**4.52b**), the diene (**4.52c**) underwent an intramolecular Diels-Alder reaction with the allene moiety leading to the steroid-like scaffold (**4.52**) in 42% yield.

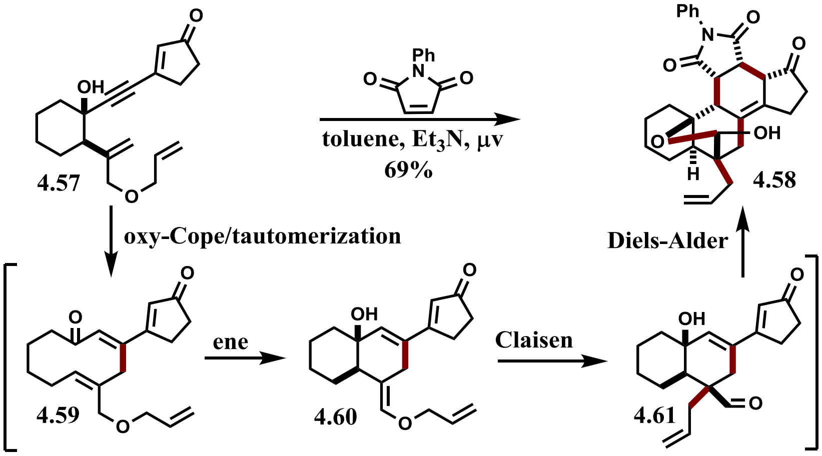
In 2001, Sherburn reported a domino intramolecular Diels–Alder reaction allowing the formation of the tetracyclic D-homosteroids core (**4.54**) from a linear precursor (**4.53**).[37] The domino intramolecular Diels–Alder reaction proceeded with 1.9 equivalents of Et_2AlCl in refluxing dichloromethane to afford three diastereoisomers in a 74:12:14 ratio with a 80% combined yield. In 2004, Pattenden and co-workers completed a short synthesis of estrone using a radical cascade. Radical precursor iodide (**4.55**), was treated with Bu_3SnH-AIBN in refluxing toluene to give the tetracyclic steroid precursor (**4.56**) in a modest 13% yield.[38] This reaction proceeds via an initial macrocyclization of the primary radical to give the tertiary radical followed by the fragmentation of the cyclopropane ring which serves to move the radical to the benzylic position. Two sequential transannular cyclizations followed by the reduction of the resulting secondary radical gave the tetracyclic steroid precursor (**4.56**) in 13% yield. The relatively slow rate of the macrocyclization allows the direct reduction of the primary radical by Bu_3SnH to compete.



Sherburn's zipper-mode domino intramolecular Diels-Alder **Pattenden's radical macro and transannular cyclizations cascade**

Scheme 4.10 *Synthesis of polycyclic steroid-related scaffolds from simple linear precursors*

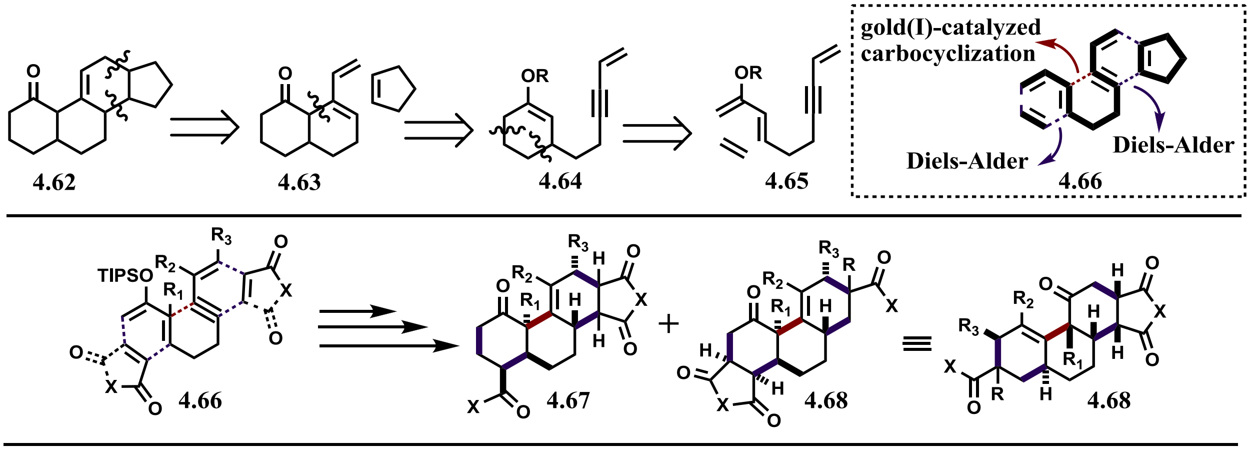
Finally, our group has developed a stereoselective synthesis of complex polycyclic compounds (**4.58**) via a domino pericyclic oxy-Cope/ene/Claisen/Diels-Alder reaction of precursor (**4.57**).[39] This impressive reaction cascade, which monitoring seven stereocenters, includes four different pericyclic reactions in a single operation.



Scheme 4.11 *Barriault's domino pericyclic oxy-cope/Ene/Claisen/Diels-Alder cascade*

4.4 Our approach towards the synthesis of steroid-related scaffold from linear precursors

The previous chapter of this thesis ended with the synthesis of a synthetically useful diene (**4.63**) via our selective 6-*endo-dig* carbocyclization. Since the intermediate (**4.64**) can come from a Diels-Alder reaction, we thought of bringing together two Diels-Alder reactions and the 6-*endo-dig* carbocyclization in a one-pot process to access steroid-related compounds (**4.67**) or (**4.68**) from a simple linear diene (**4.65**). Based on our model system, the 6-*endo-dig* pathway should not proceed further through a Prins type cyclization, as observed for the 5-*exo-dig* pathway. Thus, the tetracyclic (**4.62**) related to the steroid framework could be accessed vial a Diels-Alder reaction between cyclic dienophile and diene (**4.63**). The diene intermediate (**4.63**) could be selectively accessed via the gold(I)-catalyzed carbocyclization. The main advantage of this approach is the facile modulation of the linear substrate combined with the use of various dienophiles that could easily enable an interesting library of polycyclic compounds. The main issue anticipated was the strong substrate dependency toward the 5-*exo-dig* pathway of the gold(I)-catalyzed carbocyclization possibly limiting the scope of the reaction. However, inversing the dienophile reaction sites in the Diels-Alder sequence can also increase diversity generated by this process as shown by structures (**4.67**) and (**4.68**).



Scheme 4.12 *Retrosynthectic analysis of the Diels-Alder/gold(I)-catalyzed carbocyclization/ Diels-Alder sequence*

The synthesis of various dienes (**4.65g-r**) followed a convergent approach starting from 5-pentynol **(4.72)** and different trialkyl phosphites or directly from alkyl phosphonates (**4.71**). We made β-ketophosphonates (**4.70**) through deprotonation of alkyl phosphonates (**4.71**) with *n*-butyllithium followed by acylation with methyl acetate. After oxidation of 5-pentynol with pyridinium chlorochromate in DCM to the corresponding aldehyde (**4.73**), we prepared enones (**4.69**) via a Horner-Wadsworth-Emmons reaction using sodium hydride in THF. Finally, a Sonogashira cross-coupling reaction was used to incorporate various vinyl substituents and the formation of silyl enol ether gave desired dienes (**4.65**). Dr. Revol started this project by investigating various **R2** and **R3** substitutions on substrate (**4.65b**). Later, myself and Stéphanie Lanoix (honours student) decided to expand the scope by changing the **R1** position. Our first thought was to incorporate medicinally interesting functional groups such as fluorine atom and cyclopropyl unit (**4.65e,f**). The difficulty of accessing the corresponding β-ketophosphonates leads us to limit our study to butyl, phenyl and hydrogen substituents **(4.65a,c,d)**. With these substituents, we quickly synthetized more than twelve different dienes to study the Diels-Alder/gold(I)-catalyzed carbocyclization/Diels-Alder (D.-A./6-*endo* Au/ D.-A.) sequence.

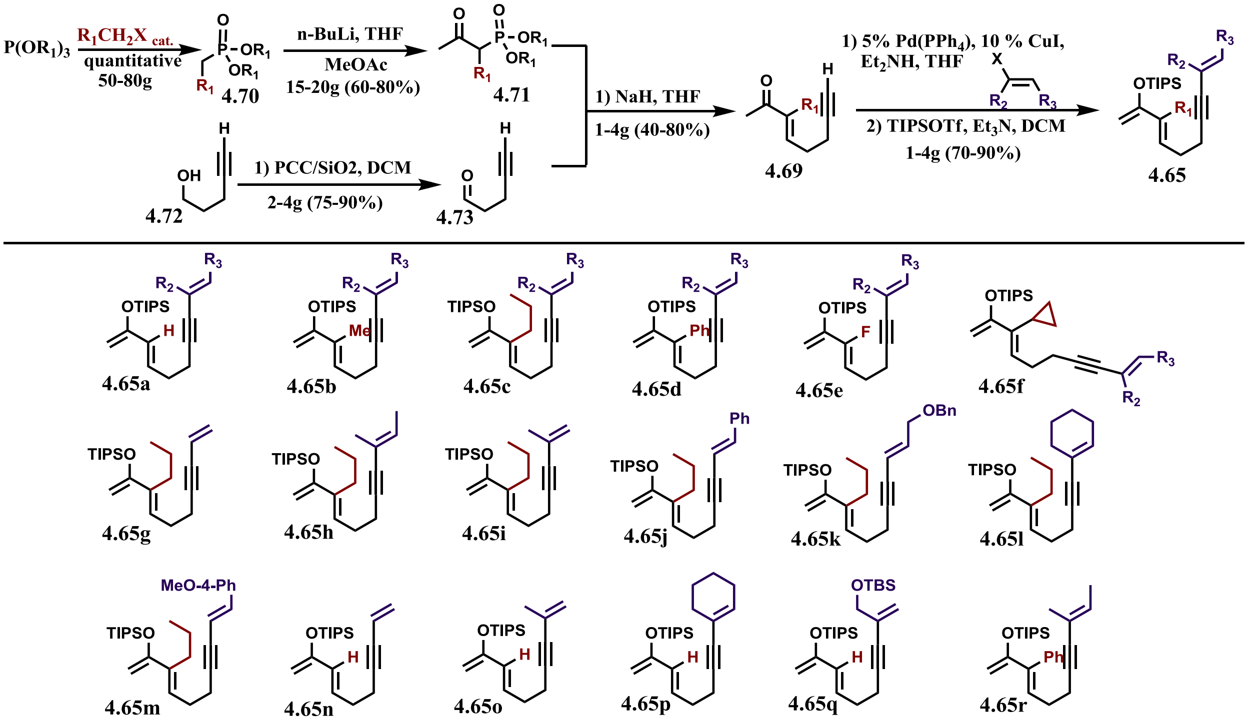
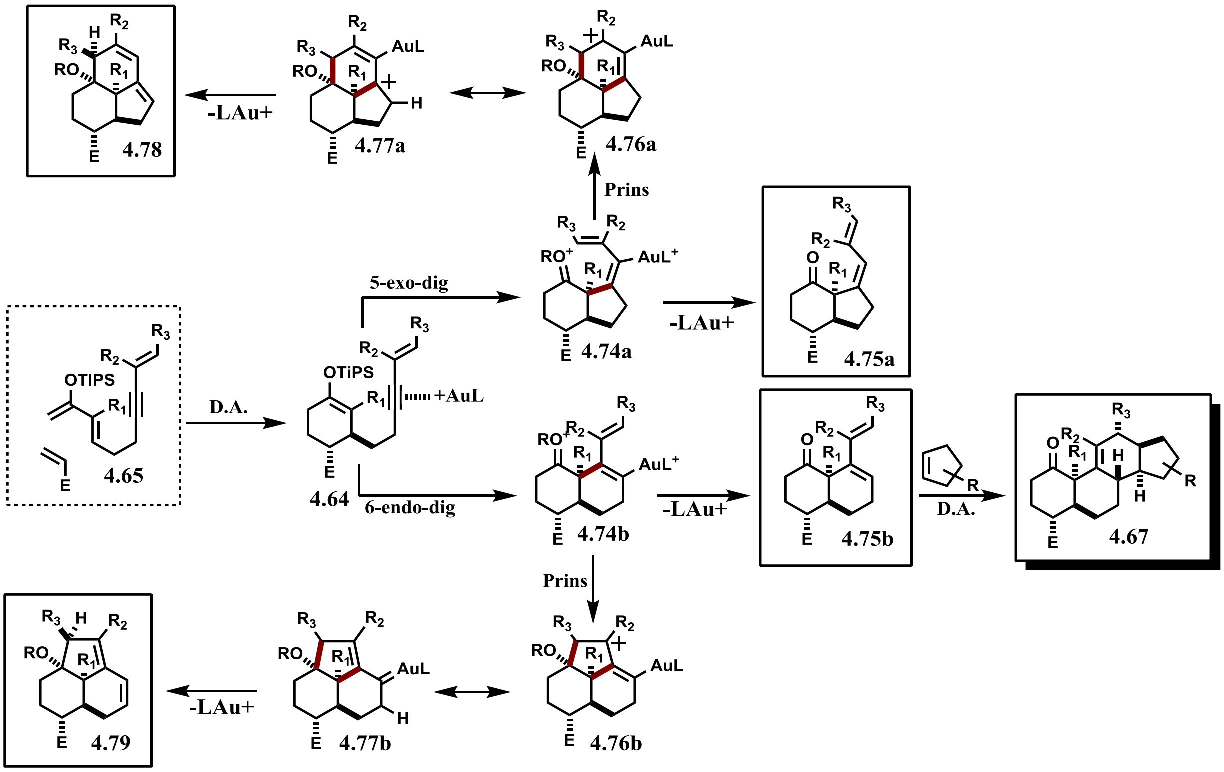


Table 4.01 *Convergent gram-scale synthesis of our linear precursors*

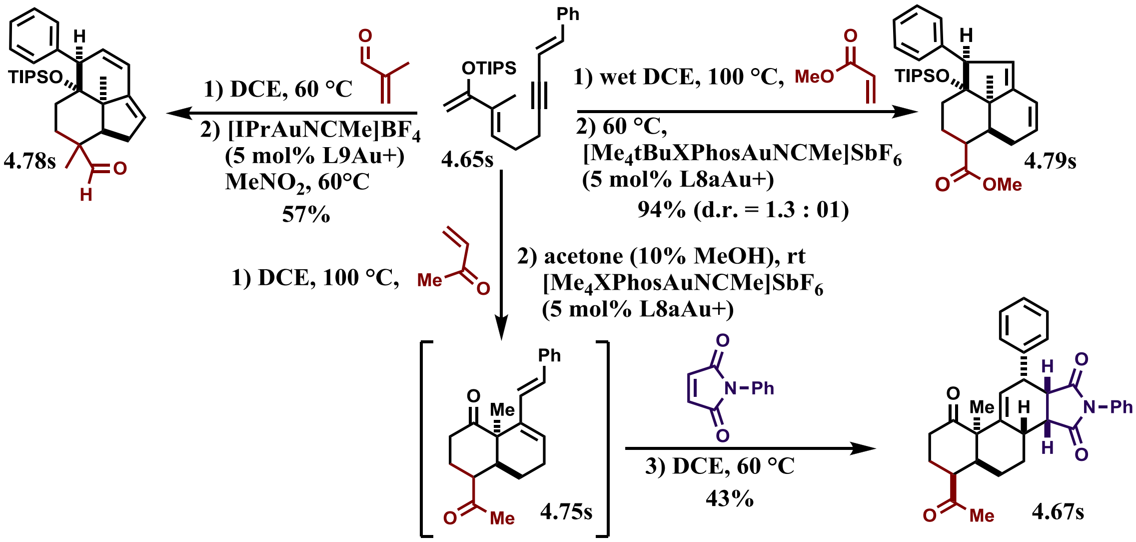
We had previously found that the gold(I)-catalyzed carbocyclization can lead to four different products. The selective synthesis of tricyclic compounds (**4.78**) and **(4.79)** resulting from a formal [3+2] or [4+2] cycloaddition can be explained by the following divergent mechanism (**Scheme 4.13**). After the first Diels-Alder reaction and complexation of the enyne by the cationic gold(I) complex, an intramolecular cyclization could take place in a 5-*exo-dig* fashion to afford the vinyl gold **(4.74a)** or via the competitive 6-*endo-dig* cyclization to access the intermediate (**4.74b**). While the regioselectivity can be strongly substrate dependent, new development in gold(I) catalysis could bring some control to overcome the preferential pathway leading to an acceptable to excellent selectivity. Instead of undergoing protodeauration followed by hydrolysis, vinyl gold dienes (**4.74a**) and (**4.74b**) can react through a Prins type cyclization on the highly electrophilic carboxonium moiety to form new cationic vinyl gold intermediates (**4.76a**) and (**4.76b**). Carbocation (**4.76a**) is stabilized by resonance giving the highly stable tertiary carbocation (**4.77a**). In the other case, the carbocation (**4.76b**) is stabilized by retrodonation from the gold(I) complex to generate carbenoid intermediate (**4.77b).** Proton elimination followed by protodeauration furnished tricycles (**4.78**) or (**4.79**), generally as a sole isomer. The *syn* geometry observed between the silyl alcohol and the group **R1**, and as well as the *trans* geometry between the silyl alcohol and the substituent **R3** can be explained via a Prins type mechanism. These two pathways are possible if the hydrolysis of the oxonium and protodeauration are slow enough to allow the Prins cyclization to occur, leading to two isomeric 6-6-5 tricycles.



Scheme 4.13 *Mechanism of the Diels-Alder/gold(I)-catalyzed carbocyclization/Diels-Alder sequence*

When the Prins cyclization is not competitive, vinyl gold dienes (**4.74a**) or (**4.74b**) undergo hydrolysis and protodeauration to afford dienes (**4.75a**) or (**4.76b**), respectively. The main goal of this project was to follow selectively the pathway leading to dienes (**4.75b**) in order to develop a robust and modular synthesis of polycycles (**4.67**) related to steroid framework.

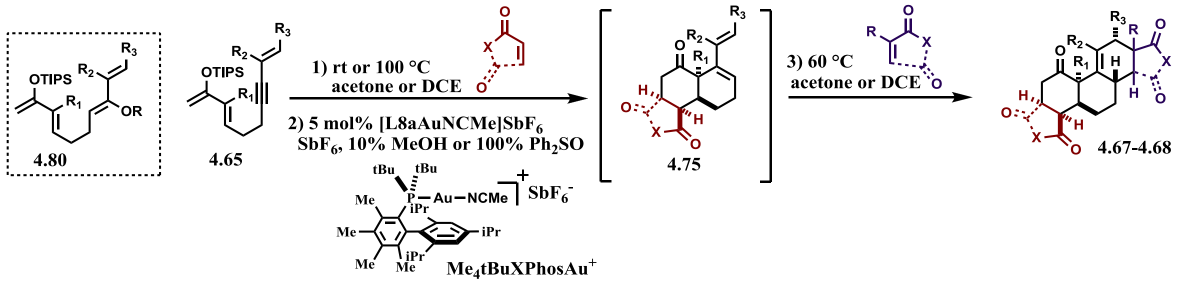
The pharmaceutical industry needs simple, flexible, and fast strategies to build a collection of natural-like products, exhibiting greater molecular diversity and complexity, from readily available starting materials. We believe that a careful tuning of the gold catalyst environment could allow full exploitation of the divergent mechanism and enable selective formation of three diterpenoid related polycycles from a single common mechanistic intermediate **(4.64).** We anticipated that the reaction conditions for the Diels-Alder reactions would be compatible with the gold(I) catalysis. As a result, this route could be adapted in a "one-pot" process from (**4.65**) to (**4.75b**), (**4.78**) or (**4.79**). One can recognize that the incorporation of Diels-Alder reactions to our strategy will add modularity and functionality while the mechanistic divergent gold(I)-catalyzed carbocyclization will adjoin framework diversity and complexity. Thus, diene (**4.65s**) was heated at 100°C with methyl acrylate in dichloromethane (0.1% H_2O) for 18 hours and then our optimal catalyst $Me_4tBuXphosAu^+$ (**L8aAu+**) was added (**Scheme 4.14**). The reaction mixture was kept stirring at room temperature for another 18 hours. We obtained predominantly the product (**4.79s**) resulting from the formal gold(I) catalyzed [3+2] cycloaddition in a modest yield of 36%.



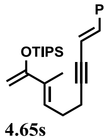
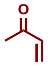
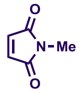
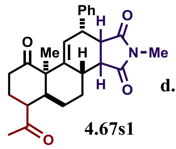
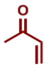
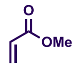
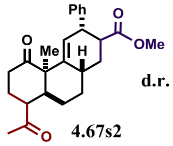
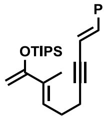
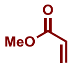
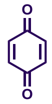
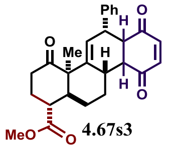
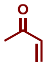
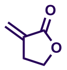
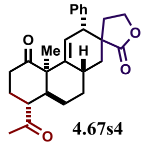
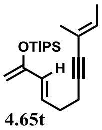
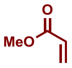
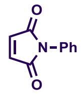
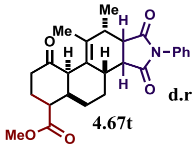
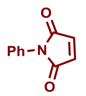
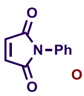
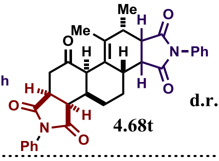
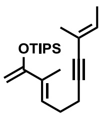
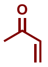
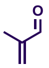
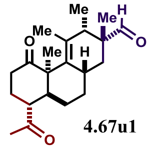
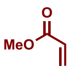
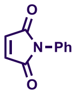
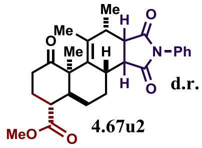
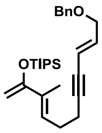
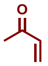
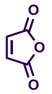
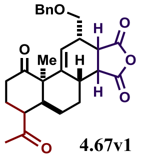
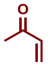
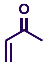
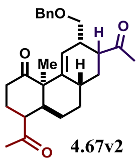
Scheme 4.14 *Building molecular diversity by gold(I)-catalysis*

We found that heating the reaction at 60°C after the addition of the catalyst favored the formation of (**4.79s**) in a 94% isolated yield with a ratio 6:1 over the other tricycle (**4.78s**). In order to control the different pathways of the mechanism, we examined various ancillary ligands and reaction conditions. Dr Guillaume Revol demonstrated that the one pot reaction carried out in nitromethane and in the presence of IPr gold complex (**L9Au+**) gave exclcusively the 5-*exo-dig*/formal [4+2] cycloaddition product (**4.78s**) (**Scheme 4.14**). One of the biggest challenges that we encountered was to selectively favour the formation of diene (**4.75**), over the tricyclic compound (**4.79**). As the rate limiting step could probably be the protodemetallation, further investigation was necessary.[40] We discover that the gold(I) catalysis step performed with Me_4tBuXphosAu$^+$ (**L8aAu+**) in acetone with 10% MeOH at room temperature increase the rate of the protodeauration and the formation of the desired diene (**4.75s**). A second Diels-Alder reaction was then easily performed on the crude reaction mixture in DCE with *N*-phenylmaleimide at 60 °C over 18 h. After purification, the tetracycle (**4.67s**) was isolated as two major diastereoisomer in a 43% yield. Remarkably, from the linear enol (**4.65s**), we show that a one-pot Diels-Alder/gold(I)-catalyzed carbocyclization/(Diels-Alder) sequence could selectively deliver three different polycyclic frameworks (**4.67s**), (**4.78s**) and (**4.79s**).

The development of a general protocol avoiding the Prins-type cyclization could be a tedious and long endeavor**.** To our dismay, the solvent system (acetone with 10% methanol) used for the synthesis of product (**4.75s**) lead to the hydration of the alkyne for sillyl enol ether (**4.65t**) and (**4.65u**), when treated with the gold(I) catalyst (**L8aAu+)**. In these cases, most of the conditions tried (acetone with water, methanol, isopropanol or *tert*-butanol, etc.) lead to the formation of the formal [3+2] product (**4.79**) and secondary product (**4.80**). Finally, we discovered that the addition of two equivalent of diphenyl sulfoxide with Me_4tBuXPhosAu$^+$ (**L8aAu+**) favored the formation of the diene (**4.75s**) and eliminating the subsequent Prins-type cyclization. The exact role of the diphenylsulfoxide is still unanswered, but we believe it shortens the lifetime of the carboxonium and avoids the Prins cyclization to occur without adding directly to the complexed alkyne, limiting the formation of side product (**4.80**). As shown in **Table 4.02**, complex carbocycles were prepared in a single operation in good diastereoselectivity and chemical yield.



4.80 4.65 4.75 4.67-4.68

entry	subtrate	dienophile 1	dienophile 2	produit	yield	entry	dienophile 1	dienophile 2	produit	yield
1	 4.65s			 4.67s1	60%, d.r. = 04: 01: 01	2			 4.67s2	57%, d.r. = 06: 01: 01
3	 4.65s			 4.67s3	28%	4			 4.67s4	33%, d.r. = 2.0 : 01
5	 4.65t			 4.67t	52%,[1] d.r. = 2.0 : 01	6			 4.68t	81%,[1] d.r. = 4.6 : 01
7	 4.65u			 4.67u1	43%	8			 4.67u2	55%, d.r. = 4.5 : 01
9	 4.65v			 4.67v1	63%, d.r. =1.6 : 01	10			 4.67v2	43% d.r. = 3.6 : 01

[1] JonhPhosAu+ (L1aAu+) was used as catalyst

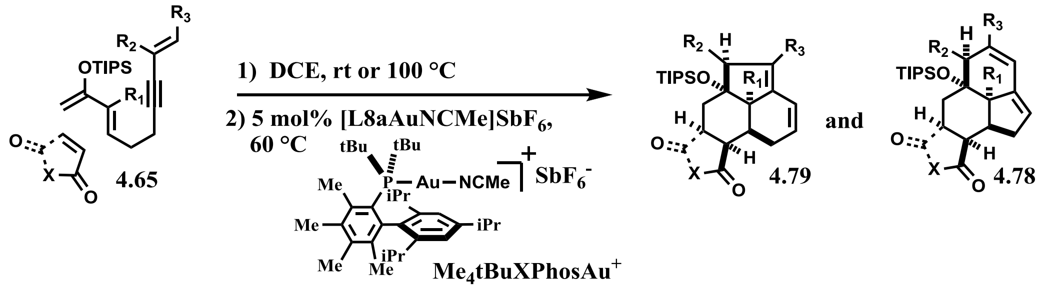
Table 4.02 *Scope of Diels-Alder/gold(I)-catalyzed carbocyclization/Diels-Alder sequence for the synthesis of steroid-related scaffold*

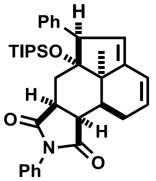
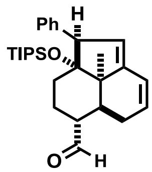
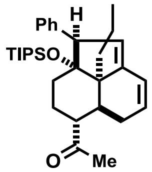
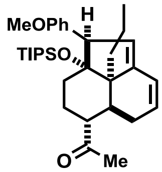
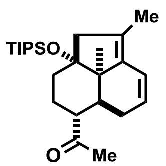
This work was done by Dr Guillaume Revol. This route proves to be versatile; as a wide variety of dienophiles: cyclic, non-cyclic, mono-substituted, and di-substituted were used for the first and the second Diels-Alder reaction. One can notice some limitations related to the moderate selectivities observed for the second Diels-Alder when maleimide, anhydride maleic or butyrolactone were used. Unlike the two diastereoisomers resulting from the first Diels-Alder which seems to epimerize when heated in presence of gold(I) catalyst, the second Diels-Alder gives *exo* and *endo* stereoisomeric mixtures in most cases. With enyne (**4.65s**), four selected examples demonstrated the broad tolerance for the second dienophile (**entries 1-4**).

Remarkably, pentacycle (**4.68t**) was obtained in an excellent 81% yield when *N*-phenyl maleimide was used for both dienophiles (**entry 6**). Benzylic protected allylic alcohol (**4.65v**) can also be used to obtain the corresponding tricycle (**4.67v2**) and tetracycle (**4.67v1**) in moderate yield (**entries 9** and **10**).

4.5 Scope of the Diels-Alder/gold(I)-catalyzed formal [3+2] and [4+2] cycloadditions

The one-pot sequence consisting of the Diels-Alder and the formal [3+2] or [4+2] gold(I)-catalyzed cycloaddition are rather flexible and robust, allowing the synthesis of varied polycyclic compounds (**Table 4.03** and **4.04**). These reactions are widely tolerant to numerous dienophile partners and diverse chains on the enyne moiety, which can be easily modulated during their synthesis. Standard conditions in DCE with $Me_4tBuXPhosAu^+$ as catalyst (**L8aAu+**) allow the synthesis of formal [3+2] cycloadduct (**4.79s2** and **3**) in excellent yield and good selectivity with linear precursor (**4.65s**). Happily, the formation of subsequent stereocenters is completely controlled by the geometry of the carbons set during the first Diels-Alder reaction. In numerous cases, we obtained a sole diastereoisomer, resulting either from a selective Diels-Alder reaction or epimerization when heated in presence of the gold(I) catalyst. The use of *n*-propane substituent at the **R1** position slightly decreases the yield of the transformation but increases the selectivity (**entries 3** and **4**). Interestingly JohnPhosAu+ catalyst (**L1aAu+)** provides the best result for product (**4.79h**) and (**4.79t**) (**entries 6** and **7**). Cyclohexene on the enyne moiety lead to exquisite selectivity for the formal [3+2] cycloaddition (**entries 8** and **9**). Some general tendencies and limits can be observed. The use of an alkyne or cyclic dienophiles disfavour the formal [3+2] cycloaddition, but acrolein and methyl vinyl ketone were suitable dienophile partners. Electron rich hindered enyne moieties favour the formal [3+2] cycloaddtion while no substituent on the enyne moiety favours the formal [4+2] cycloaddition.

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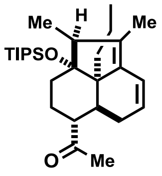
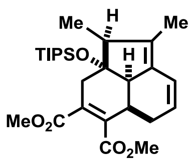
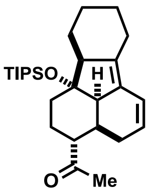
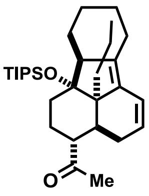
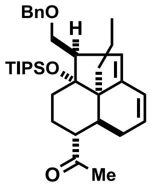
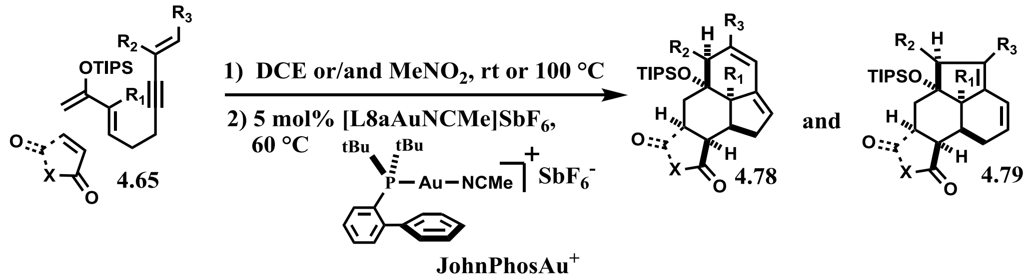
entry	**1**	**2**	**3**	**4**	**5**
yield	**95% (05:01)**	**95% (05 :01)** **d.r. = 2.5 : 01**	**66% (06 :01)**	**61% (09:01)**	**71% (03 : 01)**
					
product	**4.79h**	**4.79t**	**4.79p**	**4.79l**	**4.79k**
entry	**6[1]**	**7[1]**	**8**	**9**	**10**
yield	**65% (07 : 01)**	**74% (03 : 01)**	**67%**	**72%**	**58% (06 : 01)**

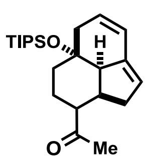
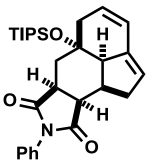
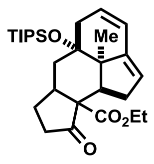
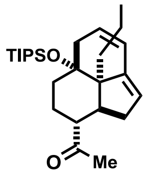
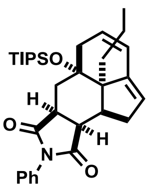
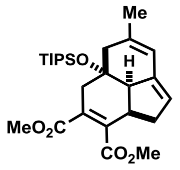
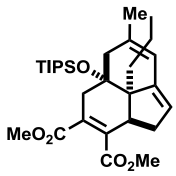
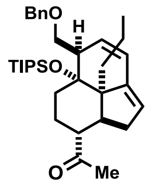
1) JonPhosAu+ (L1aAu+) was used as catalyst

Table 4.03 *Scope of the Diels-Alder/gold(I)-catalyzed formal [3+2] cycloaddition*

To our delight, unsubstituted enynes were suitable substrates for the formal [4+2] cycloaddtion (**Table 4.04**). With these linear precursors (**4.65 n, g** and **x**) in hand, we synthesized five different polycycles with good to excellent yield and selectivity (**entries 1-5**). An interesting dienophile for the synthesis of steroid related framework was used for the formation of tetracyclic product (**4.78x**). Enynes (**4.65i**) and (**4.65o**) usually lead to a complex isomeric mixture of conjugated dienes, but when dimethyl acetylenedicarboxylate was used as the dienophile, only the standard isomer was observed (**entries 6** and **7**). Finally, more challenging enyne substrate (**4.65k**) can be used in the formal [4+2] cycloaddition with acceptable level of selectivity with IPr gold(I) complex **(L9Au+)** as catalyst (**entry 8**). Thus, we have demonstrated that this simple sequence allows a quick generation of scaffold diversity and molecular complexity by a slight modification to the reaction conditions or by changing the substitution of the linear precursors.



4.65 4.78 4.79

product	 **4.78n1**	 **4.78n2**	 **4.78x**	 **4.78g1**
entry	1	2	3^1	4
yield	62% d. r. = 04 : 01	55%	84% d. r. = 1.2 : 01	81% d. r. = 09 : 01
product	 **4.78g2**	 **4.78o**	 **4.78i**	 **4.78k**
entry	5	6	7	8^1
yield	90%	63%	72%	51% (2.2 :01)

1) IPrAu+ (L9Au+) was used as catalyst and DCE/$MeNO_2$ as solvent

Table 4.04 *Scope of the Diels-Alder/gold(I)-catalyzed formal [4+2] cycloaddition*

4.6 Possible applications of the formal gold(I)-catalyzed cycloaddtion to the synthesis of natural products

Although the Prins-type cyclization is a major competitive process that could hampered the modular synthesis of steroid, one can recognize that it might be able to open up new opportunities for the synthesis of complex natural products. The tricyclic cores of various natural products, highlighted in red, could arise from a gold(I)-catalyzed formal [3+2] or [4+2] cycloaddition (**Figure 4.02**). The first row of the Figure represents diverse terpenes where the disconnection is the same as discussed previously, while the second row exhibits natural products that are in the alkaloids family and the disconnections seem less obvious. Fortunately, the framework obtained from the formal [3+2] cycloaddition natural products is embedded in neoamphilectane and stereumine H.

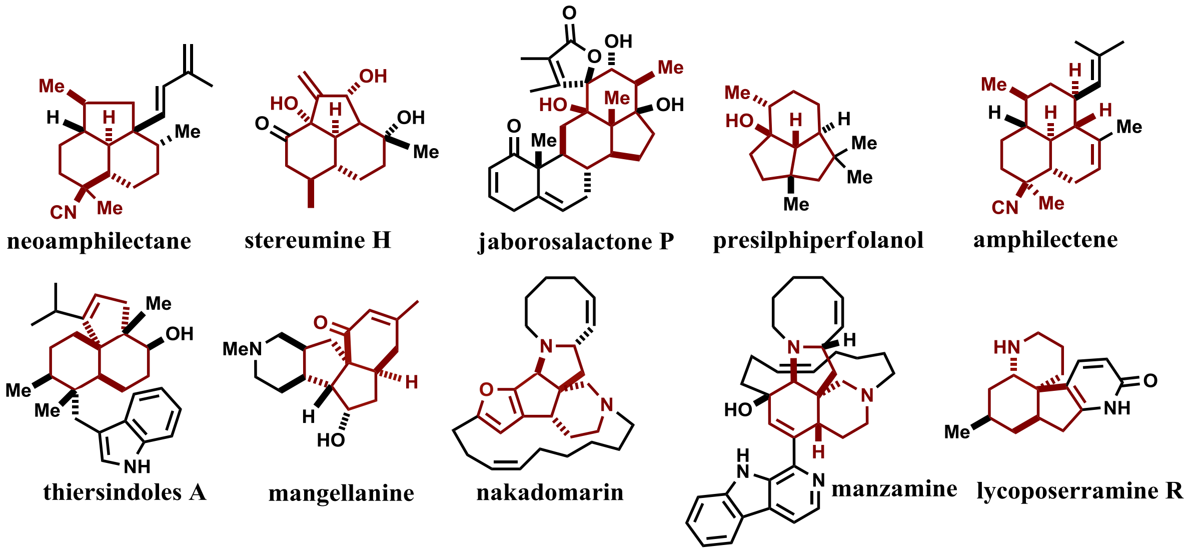
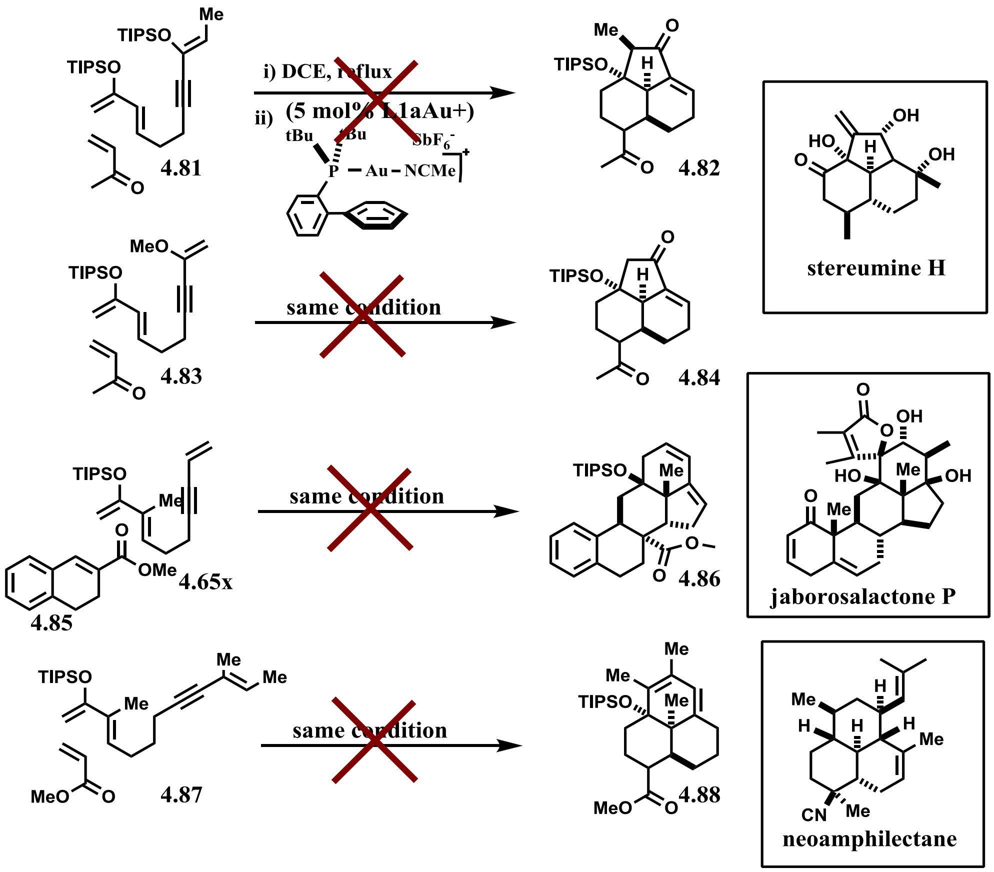


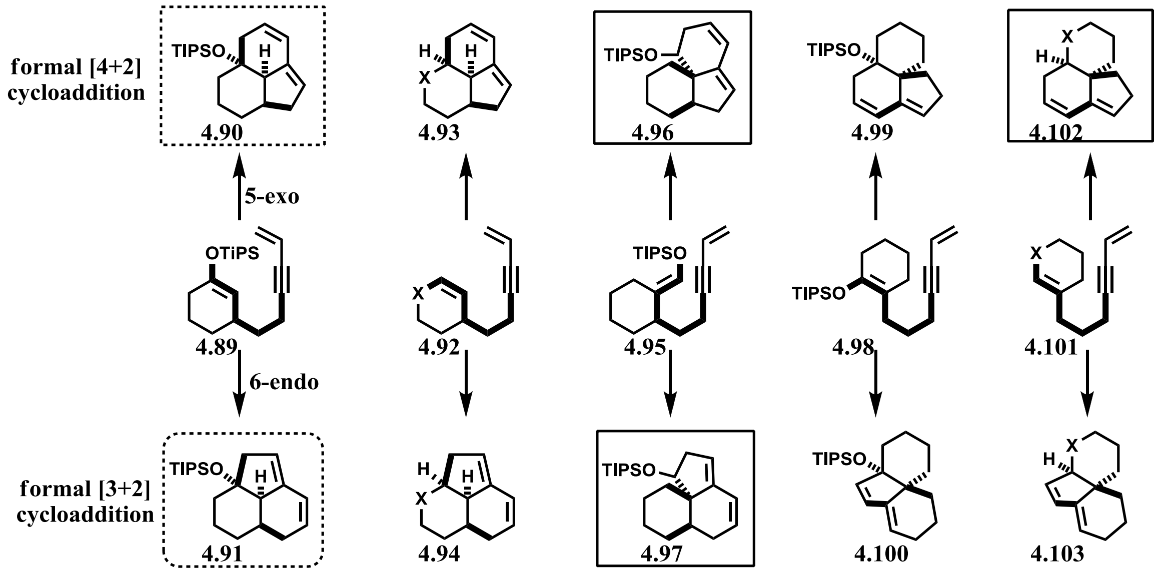
Figure 4.02 *Examples of natural producst incorporating three angular fused rings*

While, the tricyclic core of the formal [4+2] cycloaddtion can be found in the jaborosalactone P and presilphiperfolanol frameworks, the tricyclic core of amphilectene could come from an initial 6-*exo-dig* cyclization followed by the Prins-type cyclization. Stereumine H is a good target to test the robustness of the formal [3+2] process (**Scheme 4.15**). If the enyne moiety tolerates silyl enol ether, only two other oxygen atoms should be incorporated to complete the synthesis. We started the investigation with substrate (**4.81**), which contained two bulky silyl enol ethers (TIPS). Unfortunately, neither the desired product (**4.82**), nor the formation of any carbon-carbon bond during the gold(I)-catalysis step was observed. More disappointingly, the same results were found with simpler substrate (**4.83**). Despite the fact that we previously demonstrated that unsubstituted vinyl as compound (**4.65x**) underwent efficiently the formal [4+2] cycloaddition with diverse dienophiles, we never observed the framework of the natural product jaborosalactone P using dienophile (**4.85**). Surprisingly our preliminary result on the 6-*exo-dig* cyclization in order to afford fused tricycle composed only of six membered rings as compound (**4.88**) did not show any reactivity under gold(I)-catalysis.



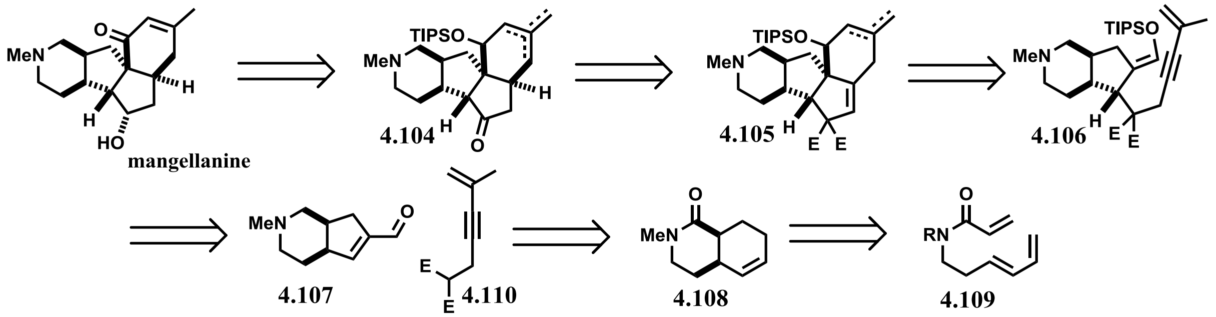
Scheme 4.15 *Failing in the synthesis of natural product frameworks*

Keeping the same 1,6 relationship between the alkene and the enyne moiety but changing the ring template allowed the synthesis of angulary fused tricycle framework with cup-shaped architectures, also found in numerous natural products. This observation allowed me to develop retrosyntheses of alkaloid natural products using the same reactivity described for the formation of terpenoid cores. The tricyclic 5-*exo-dig* core (**4.96**) can be found in magellanine and the corresponding 6-*endo-dig* core (**4.97**) can be found in thiersindoles A. A study performed with platinum(II)-catalysis revealed the usefulness of these related disconnections.[42] An enamine related to compound (**4.101**) undergoes a formal [3+2] cycloaddition under platinum(II)-catalysis, leading to the tetracyclic core of nakadomarin A **(Scheme 1.03)**. Using an equivalent strategy, but governing the mechanism towards the competitive 5-*exo-dig* pathway could enable a quick synthesis of alkaloid lycoposerramine R. On the other hand, tricyclic cores (**4.99**) and (**4.100**) which did not seem to be found in any natural frameworks could also come from a linear precursor and could be accessed via our Diels-Alder/Gold(I)-catalyzed formal cycloaddition sequence.



Scheme 4.16 *Scaffolds accessible via the gold(I)-catalyzed formal cycloaddtion*

The usefulness of the gold(I)-catalyzed formal cycloaddition to the synthesis of alkaloid natural products can be seen in the retrosynthetic analysis of mangellanine. I did not know at this time, but this molecule was already the target of colleague Genevieve Betournay. She was tackling this molecule envisioning gold(I)-catalysis as the key step, but with a completely different reactivity and disconnection. However, mangellanine could easily come from the advance polycyclic intermediate (**4.105**) with some functional group manipulations. The angulary tetracycle (**4.105**) can be broken in regards of the formal [4+2] cycloaddtion between an exo silyl enol ether and a tether enyne. Bicyclic silyl enol ether (**4.106**) can be formed via 1,4 addition of bis-stabilized nucleophilic carbanion (**4.110**) and the bicyclic enaldehyde (**4.107**). This 5,6 bicyclic system is obtained via the oxidative cleavage of olefin (**4.108**) and a subsequent intramolecular aldol condensation. Finally, the bicyclic (**4.108)** with a *cis*-junction could come from an intramolecular Diels-Alder reaction of linear compound (**4.109**).



Scheme 4.17 *Retrosynthetic analysis of magellanine using a gold(I)-catalyzed formal[4+2] cycloaddition*

4.7 Conclusion

While the ambitious vision to develop a general, robust and modular synthesis of polycyclic framework related to steroid is not yet attained, we have proved the concept and brought new opportunities for the synthesis of interesting polycyclic frameworks. Our knowledge on the selective gold(I)-catalyzed synthesis of fused carbocycle combined with the Diels-Alder reaction, allowed us to develop a new "one-pot" process for the synthesis of three different polycyclic compounds related to the terpenoid family from an unique linear precursor. The formal [3+2] and [4+2] cycloaddition tolerates various dienophiles and substitutions on the enyne. Even if preliminary application of this process to the synthesis of natural core reached some obstacles, the formal gold(I)-catalyzed cycloaddition brings new opportunity for the synthesis of polycyclic alkaloids. My primary goal in this project, the synthesis of polycyclic framework related to steroid, was found to be the biggest challenge encountered during my thesis. Controlling the formation of the first carbon-carbon bond and eliminating the Prins-type cyclization to selectively obtain the desired diene is possible but quite challenging.

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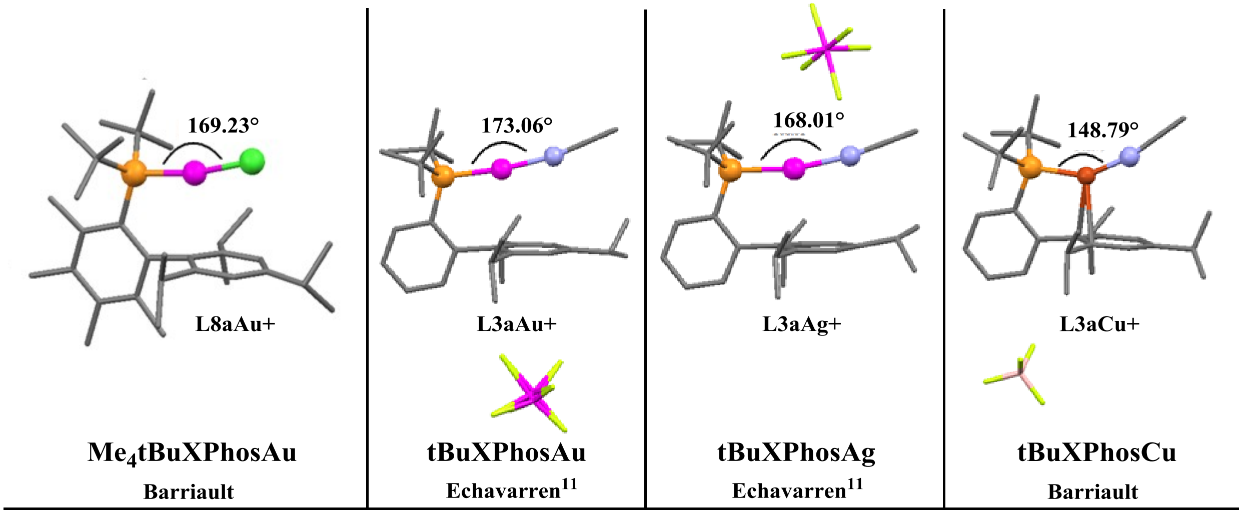
Chapter 5

Merging the Biarylphosphane Ligand Family with Silver (I) and Copper(I) Catalysis: A Complement to Gold(I) Catalysis

5.1 Introduction: Transition from gold(I) to silver(I) and copper(I)-catalysis

Gold(I) complexes are among the best catalysts for electrophilic π-activation of alkynes and possess high catalytic activity under mild reaction conditions, ultimately leading to chemoselective transformations.[1] The unique reactivity of these complexes has been rationalized by relativistic effects, which reach a maximum in the periodic table with gold atoms.[2] Relativistic effects cause the contraction of gold's empty 6s orbital, which increases π-acidity of the related complexes, as well as the expansion of the filled 5d orbitals. The 5d gold orbitals remain too low in energy to be engaged in meaningful back-bonding but the delocalization into lower energy non-bonding orbitals allows for carbenoid reactivity or cationic stabilization. Moreover, electrophilic activation proceeds in the presence of gold complexes containing donating ligands such as phosphines and NHCs, allowing the reactivity of such catalysts to be modulated in order to obtain the desired selectivity.[3] Silver, copper and gold are part of the magic triad known as "coinage metals", and the high relevance of their various metal salts in catalysis cannot be disputed.[4] As opposed to gold, the use of silver and copper electron rich phosphine complexes as catalysts has received much less attention due to their tendency to slow down or inhibit catalytic activity.[5] As these complexes are less reactive, they can potentially be more selective when the strong catalytic activity of gold complexes cannot provide an acceptable level of discrimination between two mechanistic pathways. Bulky biphenyl phosphines developed by the Buchwald group have brought unique reactivity and selectivity in palladium(0) and later in gold(I) catalysis.[6] While silver(I) salts have recently demonstrated the ability to catalyze a variety of electrophilic transformations,[7] their electron rich phosphine complexes are known to increase the nucleophilic properties of alkynyl-silver intermediate and therefore are rarely used for electrophilic π-activation of alkyne.[8]

In 2005, Echavarren and co-workers described the synthesis of a series of new gold(I) complexes armed with Buchwald-type phosphines.[9] These bulky ligands displayed enhanced catalytic activity and increased the stability of these gold complexes, resulting in a much slower decay of the active catalytic species.[10] An η^2- interaction was proposed to account for the higher stability and unique reactivity of biphenyl gold(I) complexes. However, a more recent study by Echavarren and co-workers indicated that this interaction should be very weak because the gold–arene distance is longer than the maximum estimated for a meaningful metal–arene interaction. In the same study, they also reported the synthesis of related silver(I) and copper(I) complexes and observed a significant interaction between the metal center and the aromatic ring of the dialkylbiarylphosphane ligands.[11] This interaction greatly increases the bend angle between the phosphine-metal-acetonitrile ligand bonds, as was demonstrated by crystallographic data analysis of Au(I), Ag(I) and Cu(I) tBuXPhos complexes (**Figure 5.01**). These sterically unique ligands allowed them to isolate the first dicoordinated copper(I) complex with phosphane and acetonitrile ligands.



Me$_4$tBuXPhosAu
Barriault

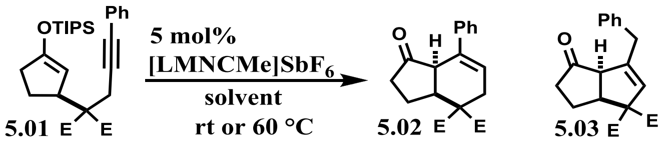
tBuXPhosAu
Echavarren[11]

tBuXPhosAg
Echavarren[11]

tBuXPhosCu
Barriault

Figure 5.01 *X-ray of cationic gold(I), silver(I) and copper (I) complexes*

During this time, we demonstrated that by adapting the ancillary ligand on the cationic gold complex, we can selectively affect the pathway for the first bond formation in the intramolecular carbocyclization of silyl enol ethers. Strong σ-donating ligand IPr (**L9**) offering a perfect linear geometry (**Table 5.01**), allowed the selective formation of fused bicycle (**5.03**) via a *5-exo-dig* carbocyclization (<95:05) in 95% yield (**entry 1**). Remarkably, the regioselectivity can be reversed with the use of the bulky ligand Me$_4$tBuXPhos (**L8a**) to favor the *6-endo-dig* product (**5.02**) (82%, 69:31) (**entry 4**). In our preliminary investigation, this complex (**L8aAu+**) exhibits the biggest distortion from the linear geometry for the phosphine-metal-ligand bond. We concluded that an increase in the distortion of the phoshine-gold-ligand angle will improve the regioselectivity for the *6-endo-dig* cyclization over the competitive *5-exo-dig* pathway (**Table 5.01**). Therefore, we hypothesized a direct relation between the P-Au-X angle and the cyclization regioselectivity (**Figure 5.01**). Taking into account the study of Echavarren, we investigated the catalytic activity of Ag(I) and Cu(I) complexes in the regioselective synthesis of fused carbocycle. To our delight, exquisite selectivity was obtained for the formation of the bicyclic carbocycle (**5.02**) using the JohnPhosAg$^+$ complex (**L1aAg+**) in wet DCE at 60 °C (**entry 5**). The replacement of JohnPhos **(L1a)** by tBuXPhos **(L2a)** led exclusively to product (**5.02**) in 82% isolated yield at room temperature (**entry 6**). These results strongly support the abovementioned hypothesis.



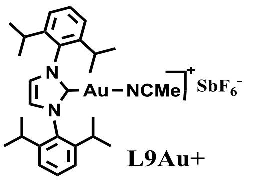
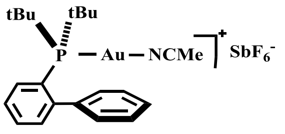
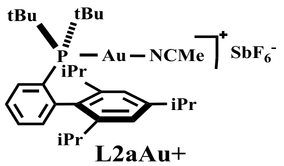
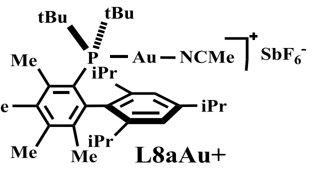
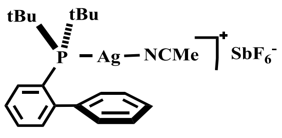
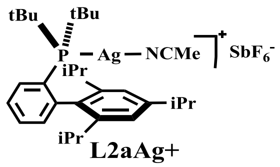
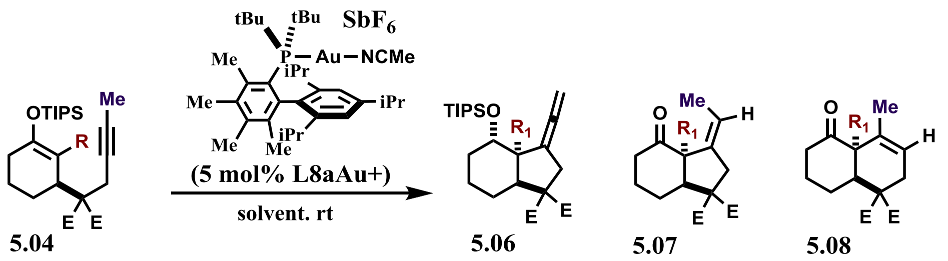
	 L9Au+	 L1aAu+	 L2aAu+
entry	**1**	**2**	**3**
ligands	**IPr**	**JonhPhos**	**t-BuXPhos**
angles	**180.00°**	**174.30°**	**173.06°**
yield%	**95%**	**86%**	**89%**
ratio	**05 :95**	**36 : 64**	**61 : 39**
	 L8aAu+	 L1aAg+	 L2aAg+
entry	**4**	**5**	**6**
ligands	**Me$_4$t-BuXPhos**	**JonhPhos**	**t-BuXPhos**
angles	**169.23°**	**165.80°**	**168.01°**
yield%	**82%**	**84%**	**82%**
ratio	**69 : 31**	**95 : 05**	**< 95 : 05**

Table 5.01 *Probing the bend angle hypothesis using silver(I)) catalysts*

Herein, we report the selective electrophilic π-activation by dicoordinated biarylphophane silver(I) and copper(I) complexes for the synthesis of fused carbocycles via a regioselective *6-endo-dig* carbocyclization. Silver(I) complexes enable the selective formation of the six-membered ring products even with the sterically and electronically neutral methyl substituent on the alkyne. Furthermore, the traditional *5-exo-dig* pathway accessed either by silver(I) and gold(I) catalysis allows the selective synthesis of two other isomeric products. Most surprisingly, very bent copper(I) complexes gives access to the *6-endo-dig* pathway on terminal alkynes without the formation of vinylidene intermediate (*vide supra*). The synthesis and investigation of silver(I) and copper(I) complexes was performed in collaboration with Patrick Levesque, a MSc student in our group.

5.2 Selective divergent synthesis of fused carbocycles: methyl substituent

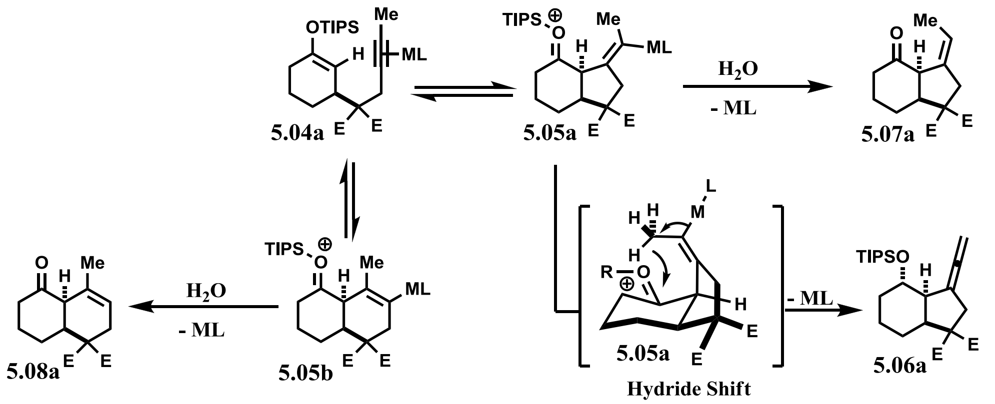
Chapter 3 described a selective *6-endo-dig* carbocyclization for internal alkynes with aryl and synthetically useful vinyl substituents. These substituents play a role in the regioselectivity of the reaction favoring the *6-endo-dig* pathway by stabilization of the cationic charge build-up on the distal carbon. The control of the regioselectivity was found to be substantially more challenging with substrates bearing a sterically and electronically neutral methyl substituent (**Table 5.02**). The Au(I)-catalyzed cyclization of substrates (**5.04 a-b**) unveiled that the substituents on the enol ether moiety greatly influence the regioselectivity of the process (**Table 5.02**). Substrates (**5.04 a** and **b**) showed the limitations of gold(I) catalysis for the synthesis of fused carbocycles. Only moderate yields and selectivities could be achieved in the synthesis of two synthetically relevant fused bicycles (**5.06**) and (**5.08**). While the *6-endo dig* product (**5.08a)** was slightly favored in acetone (57: 43) (**entry 1**), the use of DCM as solvent increased the selectivity of compound (**5.08a**) over (**5.07a**) (77: 23) (**entry 4**). Bicyclic compound (**5.06a**) containing an allene was also separated from the mixture and isolated in 18% (**entry 4**). Conversely, the cyclization of tetrasubstituted enol ether **(5.04b)** gave mainly the *5-exo dig* product (**5.07b)** regardless of the reaction conditions and the allene (**5.06b**) can be isolated in 39% yield in dichloromethane (**entries 5-8**).



entry	substrate	R	solvent	yield (5.06)	yield (5.07/5.08)
1	5.04a	H	acetone	0%	81% (43 : 57)
2	5.04a	H	DCM/acetone (20 : 01)	9%	69% (33 : 67)
3	5.04a	H	DCM/acetone (50 : 01)	15%	65% (26 : 74)
4	5.04a	H	DCM	18%	60% (23 : 77)
5	5.04b	Me	acetone	0%	82% (87: 13)
6	5.04b	Me	DCM/acetone (20 : 01)	23%	66% (83 : 17)
7	5.04b	Me	DCM/acetone (50 : 01)	28%	58% (62 : 38)
8	5.04b	Me	DCM	39%	42% (73 : 27)

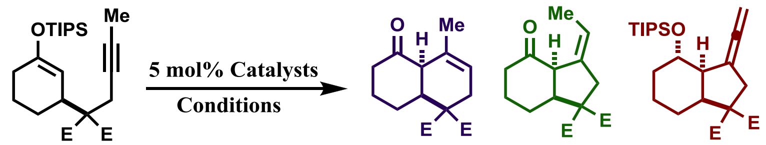
Table 5.02 *Solvent effect on the product distribution in the gold(I)-catalyzed synthesis of fused carbocycles*

Interestingly, the use of dry and hydrophobic solvent such as dichloromethane increased the formation of allene (**5.06**) possessing a stereodefined protected secondary alcohol. The formation of allene (**5.06**) is explained with the following mechanism (**Scheme 5.01**). The complexation of the cationic gold species with alkyne (**5.04**) triggers the cyclization to give the vinylgold intermediate (**5.05a**). In the absence of water, a stereospecific competing [1,5]-hydride shift affords the allene (**5.06**). At first glance, the concentration of water did not impact the regioselectivity between the *6-endo-dig* and the *5-exo-dig* pathway. Dry conditions favored allene (**5.06**), whereas hygroscopic solvents such as acetone restored the competitiveness of the protodeauration, affording bicycle (**5.07**). The regioselectivity for the first bond formation did not vary with the concentration of water in the reaction solvent, but the third product (**5.06**) was easily purified from the chromatographically inseparable mixture of compounds (**5.07**) and (**5.08**).



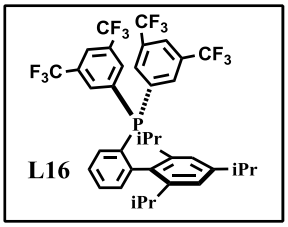
Scheme 5.01 *Proposed mechanism for the formation of allene and the stereospecific oxocarbenium reduction*

Drawing inspiration from the results shown in **Table 5.01** (**entries 5** and **6**), we examined the effectiveness of phosphino-Ag(I) catalysts on the carbocyclization of alkynes having a methyl at the terminal position. In order to provide a complete picture, we included results from our gold(I) investigation in this optimization (**Table 5.03**). As previously established, NHC gold(I) complex IPr (**L9Au+**) in acetone furnishes the *5-exo-dig* carbocyclization product (**5.07a**) in good yield and selectivity, 88% (13:87) (**entry 1**). Conversely, the cyclization using $Me_4tBuXPhosAu(I)^+$ (**L8aAu+**) in acetone led roughly to an equal mixture of regioisomers favoring slightly the *6-endo-dig* product (**5.08a**) (**entry 2**). Switching acetone for dry DCM did not increase the selectivity for the *6-endo-dig* pathway, however, we did observe the formation of allene (**5.06a**) (**entry 3**). Interestingly, the use of cationic $JohnPhosAg(I)^+$ (**L1aAg+**) in DCE/H_2O afforded a mixture composed almost equally of products (**5.06a**) and (**5.08a**) (**entry 4**). More disappointingly, the use of the bulkier $tBuXPhosAg(I)^+$ (**L2aAg+)** complex favors the hydride shift product (**5.06a**) over the desired bicycle (**5.08a**) (75: 25) (**entry 5**). The exclusive formation of (**5.06a**) over (**5.07a**) caught our attention because this *5-exo-dig* pathway product (**5.06a**) is typically formed using dry condition. With 5% v/v of water in DCE, the solvent is saturated with water and therefore we expected the formation of (**5.07a**).



5.04a **5.08a** **5.07a** **5.06a**

entry	ligand	metal	catalyst	conditon	yield%	ratio
1	IPr	Au	L9Au+	acetone,rt	88%	13 : 87 : 00
2	Me$_4$tBuXPhos	Au	L8aAu+	acetone, rt	82%	57 : 43 : 00
3	Me$_4$tBuXPhos	Au	L8aAu+	DCM, -10 °C	78%	59 : 14 : 27
4	JonhPhos	Ag	L1aAg+	DCE/H$_2$O, 60 °C	76%	46 : 00 : 54
5	tBuXPhos	Ag	L2aAg+	DCE/H$_2$O, 60°C	98%	25 : 00 : 75
6	tBuXPhos	Ag	L2aAg+	DCE/H$_2$O, 60°C*	98%	31 : 00 : 69
7	tBuXPhos	Ag	L2aAg+	DCE, 60°C	90%	00 : 00 : 100
8	JackiePhos	Ag	L3gAg+	DCE/H$_2$O, 60°C	98%	85 : 00 : 15
9	JackiePhos	Ag	L3gAg+	DCE/H$_2$O, rt	75%	87 : 00 : 13
10	L16	Ag	L16Ag+	DCE/H$_2$O, rt	36%	82 : 00 : 18
11	JackiePhos	Cu	L3gCu+	DCE/H$_2$O, rt	29%	77 : 00 : 23

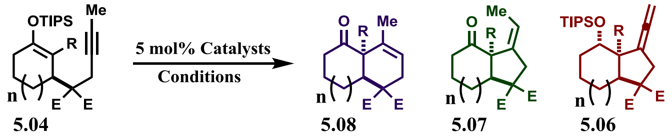


***run with 10% v/v of water in DCE**

Table 5.03 *Optimization for the selective synthesis of three different fused carbocycles*

Nonetheless, we performed analogous experiments with less and more water content. When the reaction was run in 10% v/v of water in DCE, only a slight increase in the ratio of (**5.06a: 5.08a**)was observed (**entry 6**). Interestingly, allene **(5.06a)** was isolated in high yield when a minimum amount of water (0.1% v/v) was used (**entry 7**). At this stage, we suspected that the preferential formation of allene **(5.06)** could be the result of a slower protodemetallation, which would lead to a displacement in the equilibrium towards the *5-exo-dig* pathway. In order to accelerate the protodemetallation, we introduced a more acidic source of protons in the reaction medium. Unfortunately, all these attempts resulted in the hydrolysis of the starting material (**5.04a**). The hydride shift drives the equilibrium, therefore bulkier catalyst will not help to favor decalin (**5.08a**). We then hypothesized that an electron withdrawing ligand would decrease the electronic density of the carbon-metal bond, thereby, slowing down the hydride shift. A good electronic balance must be found, the electron poor ligands also slow the protodeauration. Our first choice was JackiePhos (**L3g**), as this ligand possesses two strongly electron withdrawing aryl groups, while also keeping the essential rigidity of the biphenyl moiety. To our delight, the decalin (**5.08a**) was isolated in 98% yield as the major product in an 85:15 ratio using JackiePhos silver(I) complex (**L3gAg+**) (**entry 8**).

Although a lower chemical yield was observed, a slightly better selectivity was obtained when the reaction was run at room temperature (**entry 9**). We synthesized an analogue of JackiePhos, ligand **L16**, which lacks the two methoxy substituents on the first aryl of the biphenyl and maded the copper(I) version (**L3gCu+**) of JackiePhos. Both catalyst, **L16Ag**$^+$ and JackiePhosCu$^+$ (**L3gCu+**), caused the hydrolysis of substrate (**5.04a**) and only offered a low yield of the desired products (**5.06a**) and (**5.08a**) (**entries 10-11**). Moreover, these catalysts were less selective towards the *6-endo-dig* pathway.



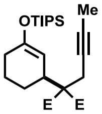
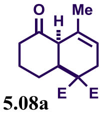
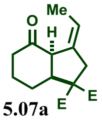
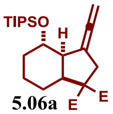
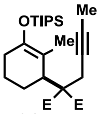
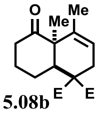
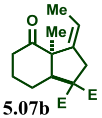
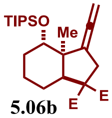
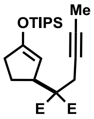
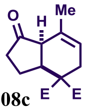
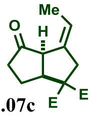
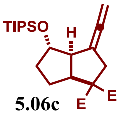
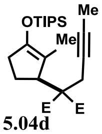
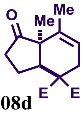
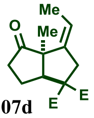
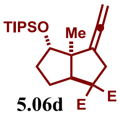
entry	substrat	condition	produit	yield
1	 **5.04a**	JackiePhosAg, DCE/H$_2$O, 60 °C	 **5.08a**	98% (85 : 15)
2		IPrAu, acetone, rt	 **5.07a**	88% (87 : 13)
3		tBuXPhosAg, DCE, 60 °C	 **5.06a**	90%
4	 **5.04b**	JackiePhosAg, DCE/H$_2$O, 60 °C	 **5.08b**	82% (42 : 58)
5		JohnPhosAu, acetone, rt	 **5.07b**	88% (90 : 10)
6		IPrAu, acetone, rt		86% (<95 : 05)
7		tBuXPhosAg, DCE. 60 °C	 **5.06b**	86%
8	 **5.04c**	JackiePhosAg, DCE/H$_2$O, 60 °C	 **5.08c**	87% (<95 : 05)
9		IPrAu, acetone, rt	 **5.07c**	86% (<95 : 05)
10		Me$_4$tBuXPhosAu, acetone, rt		81% (85 : 15)
11		tBuXPhosAg, DCE. 60 °C	 **5.06c**	78%
12	 **5.04d**	Me$_4$tBuXPhosAu, DCM, -10C	 **5.08d**	83% (97 : 03)
13		JackiePhosAg, DCE/H$_2$O, 60 ° C		80% (<95 : 05)
14		IPrAu, acetone, rt	 **5.07d**	94% (92 : 08)
15		tBuXPhosAg, DCE. 60 °C	 **5.06d**	75%

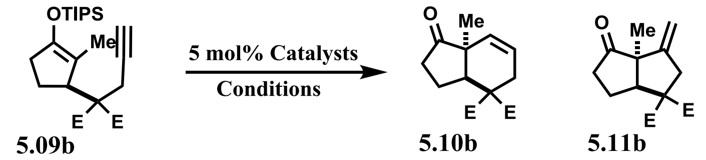
Table 5.04 *Scope of the selective divergent synthesis of fused carbocycles*

The scope of the synthesis of fused carbocycles shows the potential of silver(I) catalysis to complement gold(I) catalysis in the context of electrophilic π-activation of alkynes (**Table 5.04**). The use of the ligand IPr (**L9**) in the gold(I) complex furnishes good selectivity for the *5-exo-dig* product, regardless of which substrate is used (**entries 2, 6, 9** and **14**). As protodemetalation can be the rate-determining step, the use of dry conditions is often detrimental to catalytic processes.

Using tBuXPhosAg(I)$^+$ **(L2aAg+)** with dry DCE slowed down the protodemetalation, favoring the hydride shift from being the only accessible pathway and therefore provided the corresponding allene with good to excellent yields(**entries 3, 7, 11,** and **15**). We proposed that the electron poor JackiePhos (**L3g**) ligand disfavored the hydride shift and favored the *6-endo-dig* pathway. Five-membered ring templates afforded good selectivities with tri and tetra-substituted silyl enol ethers (**entries 8, 12, 13**). Disappointingly, the six-membered ring tetra-substituted silyl enol ether (**5.04b**) afforded the desired decalin (**5.08b**) as the minor product (42: 58) in 82% isolated yield (**entry 4**). Nevertheless, silyl enol ether (**5.04a**) furnished the *6-endo-dig* product (**5.08a**) in high yield and regioselectivity, 98% (85: 15) (**entry 1**). In Complement to gold(I) catalysis, silver(I) catalysis allowed the selective synthesis of eleven of twelve possible products, provided from four different substrates, where each substrate brought its own inherent preferential regioselectivity.

5.3 Selective synthesis of fused carbocycles with terminal alkyne

Upon exploring the scope of the silver(I)-catalyzed cyclization, we examined the metal-catalyzed cyclization of enol ethers with terminal alkyne (**Table 5.05**). It is well established that terminal alkynes undergo exclusively *5-exo-dig* cyclizations using Au(I), Hg(II) and Pt(II) catalysts.[12] As expected, the cyclization of (**5.09b**) in the presence of 5 mol% of the cationic Me_4tBuXPhosAu(I) (**L8aAu+**) afforded exclusively bicycle (**5.11b**) in 95% yield (**entry 1**). Without any expectations, we investigated whether silver(I) and copper(I) complexes could provide a different outcome. It is with great surprise that we observed, using the JohnPhosAg(I)$^+$ catalyst (**L1aAg+)**, a ratio of 21:79, albeit in low yield and favoring the *5-exo-dig* product **(5.11b)** over the desired bicycle **(5.10b)** (**entry 2**). While compound (**5.11b**) was still the major product, an excellent 92% yield (34: 66) was obtained using the tBuXPhos (**L2a**) ligand (**entry 3**). Reducing the water content to 0.1% v/v slightly increased the yield to 99%, but slightly decreased the regioselectivity (38:61) (**entry 4**). BrettPhosAg$^+$ **(L3aAg+)** and JackiePhosAg$^+$ (**L3gAg+**) complexes proved to be less satisfactory ligands (**entries 5** and **6**). While the electron withdrawing biarylphosphine JackiePhos (**L3g**) seemed to be the least selective ligand for the *6-endo-dig* cyclization of (**5.09b**), we assumed that, in this case, bulky and electron rich Me_4tBuXPhos (**L8a**) would be ideal to enhance the selectivity.

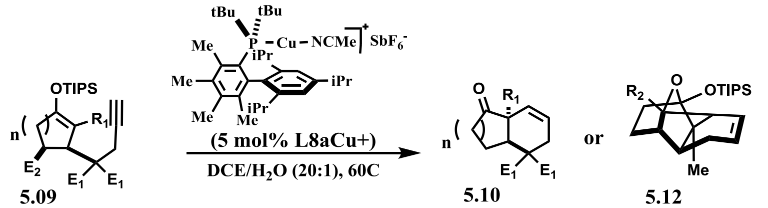


entry	ligand	metal	catalyst	conditon	yield%	ratio
1	Me_4tBuXPhos	Au	L8aAu+	acetone, rt	95%	00 : 100
2	JohnPhos	Ag	L1aAg+	DCE/H_2O, 60 °C	43%	21 : 79
3	tBuXPhos	Ag	L2aAg+	DCE/H_2O, 60°C	92%	34 : 66
4	tBuXPhos	Ag	L2aAg+	DCE/H_2O, 60°C	99%	38 : 61
5	BrettPhos	Ag	L3aAg+	DCE/H_2O, 60°C	94%	43 : 57
6	JackiePhos	Ag	L3gAg+	DCE/H_2O, 60°C	64%	11 : 89
7	Me_4tBuXPhos	Ag	L8aAg+	DCE/H_2O, 60°C	91%	48 : 52
8	Me_4tBuXPhos	Ag	L8aAg+	DCE/H_2O, rt	93%	51 : 49
9	Me_4tBuXPhos	Cu	L8aCu+	DCE/H_2O, 60°C	90%	61 : 39
10	Me_4tBuXPhos	Cu	L8aCu+	DCE/H_2O, rt	92%	63 : 37

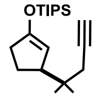
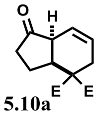
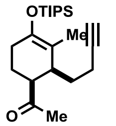
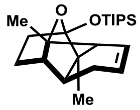
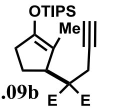
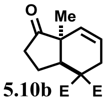
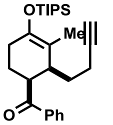
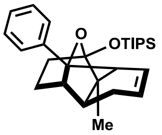
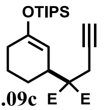
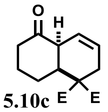
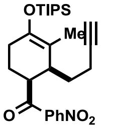
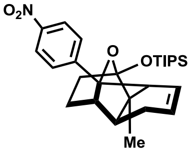
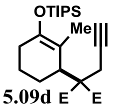
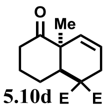
Table 5.05 *Optimization of the copper(I)-catalyzed 6-endo-dig carbocyclization of terminal alkyne*

Indeed, this was the case as we obtained (**5.10b**) and (**5.11b**) in 91% yield in a ratio of 48:52 (**entry 7**). When the reaction was performed at room temperature, an increase of selectivity to 51:49 slightly favouring (**5.10b**) was obtained, thus achieving, for the first time, a ratio favouring the endocyclic product on terminal alkynes (**entry 8**). During our research, we were unable to discover a better ligand than Me_4tBuXPhos (**L8a**), for this purpose we directed our attention towards the corresponding copper(I) complexes. Without hesitation, we tested the Me_4tBuXPhosCu^+ complex (**L8aCu+**) and we were pleased to observe that at 60°C, we increased the ratio, favouring (**5.10b**) to 61:39, altogether with a 90% yield (**entry 9**). Lowering the temperature to room temperature allowed for both an increased ratio of 63:39 and yield of 92% (**entry 10**).

Over time, we observed regioselectivity preferences inherent to substrate in the carbocyclization of non-terminal alkynes. In our model systems with a malonate tether, the five-membered rings with tetra-substituted silyl enol ether allowed the easiest access to the *6-endo-dig* pathway, while the tri-substituted silyl enol ether was typically more inclined to favor the *5-exo-dig* pathway. However, the cyclization of 6-membered ring tetra-substituted silyl enol ether with the formation of a quaternary center at the ring junction is still an unresolved challenge. We were surprised to observe a slightly better ratio in favor of the *6-endo-dig* product for susbtrate (**5.09a**) than for substrate (**5.09b**) (**Table 5.06, entries 1** and **2**). As expected, the six membered-ring template with a trisubstituted enol ether (**5.09c**) provided good selectivity to furnish decalin (**5.10c**), while only 10% of the desired product (**5.10d**) was observed with the tetra-substituted enol ether (**5.09d**) (**entries 3-4**).



5.09 5.10 5.12

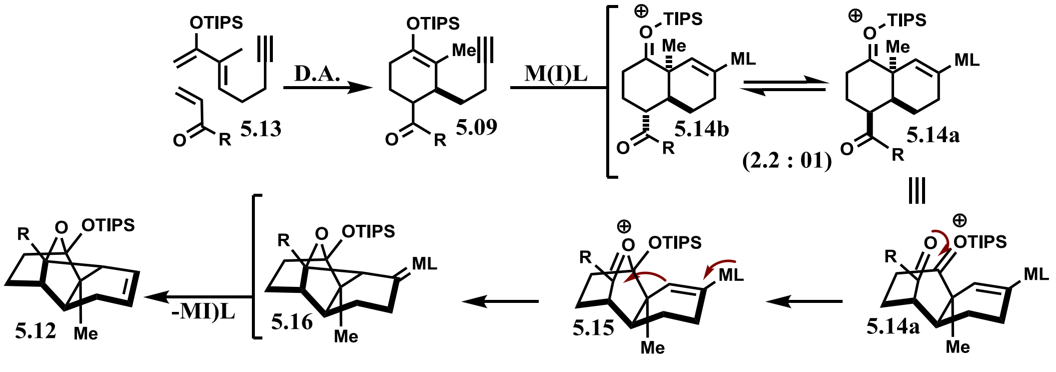
entry	substrate	product	yield	entry	substrate	product	yield
1	 5.09a	 5.10a	83% (65:35)	5	 5.09e	 5.12e	82%[a]
2	 5.09b	 5.10b	93% (63:37)	6	 5.09f	 5.12f	69%[a]
3	 5.09c	 5.10c	60% (80:15)	7	 5.09g	 5.12g	52%[a,b]
4	 5.09d	 5.10d	62% (12:88)				

a) L2aAg+ was used as catalyst, b) intermediate purified

Table 5.06 *Scope of the copper(I)-catalyzed 6-endo-dig carbocyclization of terminal alkynes*

During our study on building molecular diversity by gold(I)-catalysis, we took advantage of the divergence offered by the catalytic cycle to build diverse and distinct molecular scaffolds from a single common mechanistic intermediate (**Chapter 4, Section 4.4** and **4.5**). Our common intermediate arises from a Diels-Alder reaction and is closely related to substrate (**5.09e**). This intermediate has already been used in the development of a zinc- mediated cascade reaction to access hydridane core via a *5-exo-dig* cyclization.[13] Our previous study revealed that this system, without the *gem*-dimalonate, showed reverse substrate dependency with regard to the substitution of the silyl enol ether; formation of the vicinal quaternary center, on this scaffold, favors the *6-endo-dig* pathway.

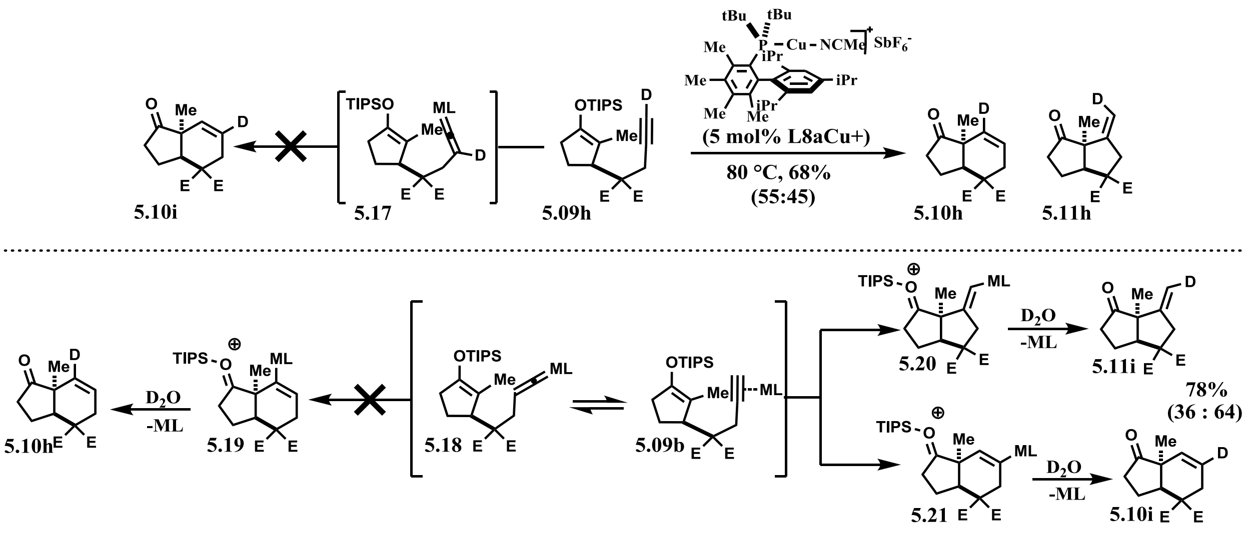
In order to rapidly expand the scope of the copper(I)-catalyzed 6-*endo-dig* carbocyclization of terminal alkyne, we attempted to cyclize intermediate **(5.09e, f** and **g)**. To our great pleasure, we isolated polycyclic product (**5.12e**), which resulted from an initial *6-endo-dig* cyclization, as a sole isomer in 82% yield (**entry 5**). Moreover, the stereospecific polycycle (**5.12e**) can easily be accessed in a one-pot process from the linear precursor (**5.13e**). The Diels-Alder reaction offers the possibility to easily modify the enone moiety. We therefore synthesized two other strained polycyclic products (**5.12f** and **g**) in moderate yield of 69% and 52%, respectively. Silver(I)-catalyst (**L2aAg+**) gives cleaner reaction and is more robust than the corresponding copper(I)-complex (**L2aCu+**). Also, the purification of the intermediate from the Diels-Alder reaction could help is some cases. This tridimensional structure can be interesting from a medicinal chemistry perspective, potentially directing aromatic moieties in a specific space. The sequence to access compounds (**5.12e-g**) started with the Diels-Alder reaction of various enones with the readily accessible diene (**5.13**). The thermal Diels-Alder gave an approximate diastereoisomeric ratio of 2:1. Subsequent addition of catalyst to the mixture followed by heating at 60 °C enabled the *6-endo-dig* carbocyclization and epimerization to the intermediate (**5.14a**). The reactive oxocarbenium, alpha to the quaternary center, can be stabilized by the ketone to generate the oxocarbenium (**5.15**). The vinyl copper(I) intermediate (**5.15**) will undergo carbon-carbon bond formation and generate the carbenoid intermdediate (**5.16**). Finally, either proton abstraction and protodecupration or 1,2-hydride shift and subsequent elimination affords polycycle (**5.12**).



Scheme 5.02 *Proposed mechanism for the formation of polycyclic compounds (5.12e-g)*

This last cascade, more specifically the position of the second carbon-carbon bond formed and location of the final olefin, suggest that access to the *6-endo-dig* pathway with terminal alkynes cannot be explained by the formation of a vinylidene complex (**5.17** and **5.19**), as was reported with other metals.

In order to reject the vinylidene mechanistic pathway, we synthesized a deuterated version of bicycle (**5.09b**), compound (**5.09h**), and we also cyclized bicycle (**5.09b**) in the presence of deuterated water. If the vinylidene intermediate (**5.17**) was formed during the process, migration of the deuterium would lead to compound (**5.10i**). As expected, products (**5.10h**) and (**5.11h**) were isolated in 78% yield (55: 45). To complete our mechanistic investigation, we deuterated vinyl copper intermediates (**5.20**) and (**5.21**) with heavy water. This time, the vinylidene pathway would have provided compound (**5.10h**), but a mixture of compounds (**5.10i**) and (**5.11i**) was isolated instead. These experiments reject the formation of vinylidene intermediate as a hypothesis for a possible mechanistic pathway.



Scheme 5.03 *Deuteration of the terminal alkyne and of the vinyl copper intermediate*

5.4 Diels-Alder/gold(I)-catalyzed carbocyclization: a useful sequence towards the sythesis of the cis-decalin members of the clerodane family

The Barriault group is well-known for the fast assembly of complex carbon frameworks, in particular polyfunctional decalin systems. In the past, the principal strategy to reach this goal was the development of pericyclic reactions occurring in cascade.[14] While these transformations are very impressive and synthetically useful, the laborious synthesis of precursors is often a major drawback. Since the beginning of our study in gold(I)-catalysis, we believed this new tool would allow us to use simpler disconnections for the synthesis of similar targets.

Moreover, the incorporation of the Diels-Alder reaction to the *6-endo-dig* carbocylization enables fast assembly of decalin scaffolds from a readily available linear precursor (**Scheme 5.04**). The *cis*-decalin framework is present in the molecular structure of various classes of natural products such as cis-clerodanes, kalihinenes, thelepoganes, cadinanes, eremophilanes and valeranones.[15] Our synthetic strategy would be particularily interesting for the synthesis of members of the *cis*-clerodane family. Clerodane terpenoids represent one of the largest families of secondary metabolites, numbering over a thousand, and are best known for their antifeedant properties.[16] Many of these diterpenes exhibit wide-ranging and interesting biological activities, such as antiviral, antitumor, antifungal, antipectic ulcer and psychotropic effects.[17]

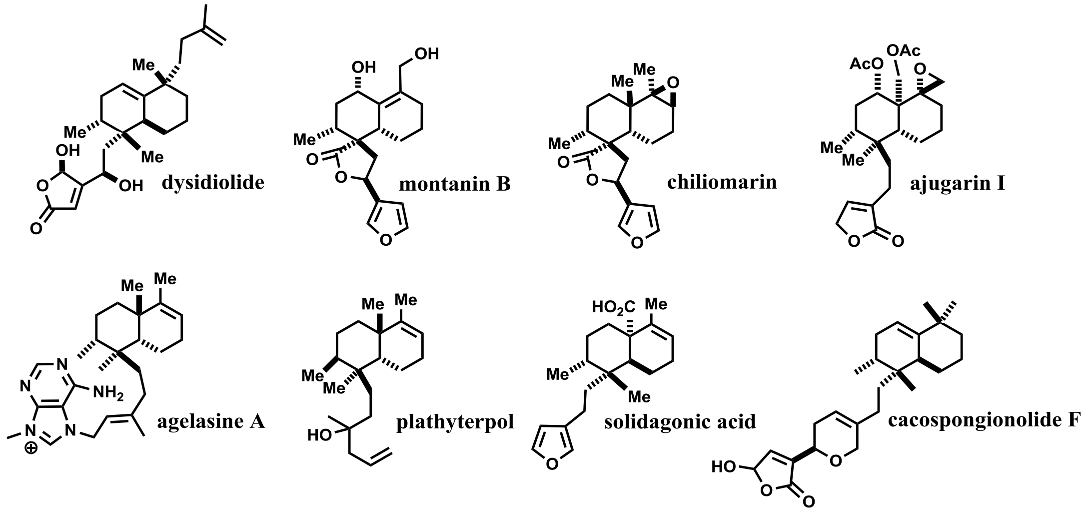
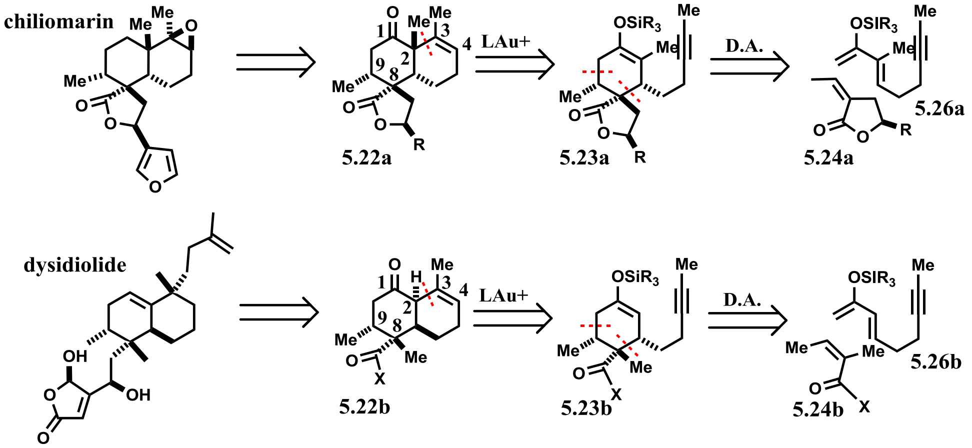


Figure 5.02 *Natural products possessing a cis-decalin scaffold*

For example, agelasine A, a *cis*-clerodane diterpene alkaloid, exhibits antimicrobial activity and strongly inhibits the activity of the enzyme Na, K-ATPase.[18] Dysidiolide, a bicyclic sesquiterpene isolated from a Caribbean sponge, which is known for its antitumor activity, has been the subject of extensive research, culminating in several total or formal total syntheses.[19] The clerodane family of natural products has received comparatively less synthetic attention. For example, only three total syntheses of clerodanes containing the γ-spirolactone moiety, a structural feature found in a large number of clerodane natural products, have been reported.[20] The total syntheses of monatanin B and chiliomarin and rapid access to its γ-spirolactone framework remain, so far, elusive to synthetic chemists .

The relatively simple decalin skeleton of clerodane related members, which may contain four to six contiguous stereogenic centers, poses a significant synthetic challenge.[21].

A general and practical synthetic approach is highly desirable and can be conceptually feasible with the combination of a sterically hindered Diels-Alder reaction and our *6-endo-dig* carbocyclization Substitution at C2 and C3 emphasizes the importance of having a regioselectively robust carbocyclization process in order to selectively obtain structurally different *cis*-decalins such as (**5.29a-b**) (**Figure 5.02)**. The intermolecular Diels–Alder reaction has been applied extensively in the construction of *cis*-decalins and has been found to be a great solution to installing the quaternary center C8 alpha to the ring junction.[22]

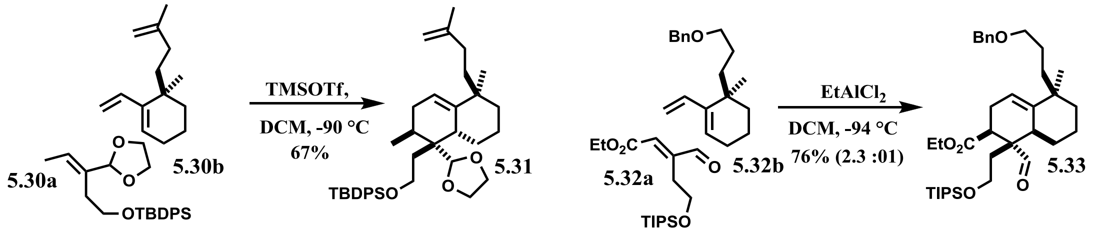


Scheme 5.04 *Retrosynthetic proposal of chiliomarin and dysidiolide: Diels-Alder/gold(I)-catalyzed carbocyclization sequence*

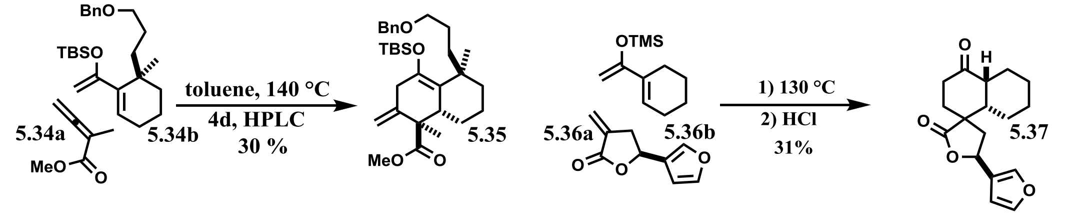
To illustrate the generality offered by our Diels-Alder/gold(I)-catalyzed carbocyclization sequence, we proposed the retrosyntheses of chiliomarin, which includes the γ-spirolactone moiety, and the retrosyntheses of dysidiolide **(Scheme 5.04)**. The installation of different functional groups on C1-C4 could easily be obtained from an olefin and a ketone respectively, as seen in intermediate (**5.22**). Intermediate (**5.22**) can be accessed via our selective gold(I)-carbocyclization and the disconnection of C2 and C3 brings back to the internal 1,6 silyl enynol ether (**5.23**). As demonstrated in Chapter 4, these cyclohexenes (**5.23**) can come from a Diels-Alder reaction between readily available silyl enol ether diene (**5.26**) and trisubstituted dienophile (**5.24**). The realization of such hindered Diels-Alder reaction with silyl enol ether is not obvious, result from the literature will be describe in the next section.

5.5 Synthesis of cis-decalins: precedents for Lewis acid catalyzed sterically hindered Diels-Alder reactions

Sterically hindered Diels-Alder reactions have been applied successfully to the synthesis of dysidiolide.[23] Tri-substituted dienophiles are known to undergo Lewis acid-mediated Diels-Alder reactions with vinylcyclohexene, even at low temperature. In 1998, a year after the first total synthesis of dysidiolide by Corey and Roberts, two different groups used this strategy to achieve their own synthesis of dysidiolide (**Scheme 5.05**).[19a-23] These convergent reactions, which install three on four stereogenic centers in the decalin scaffold, allow short and pratical syntheses (18 and 13 steps). Danishefski used a Gassman dienophile, while Boukouvalas used a doubly activated dienophile (**Scheme 5.05**). The introduction of silyl enol ether into the diene moiety should favor a greater electronic compatibility of the diene and the dienophile, while offering another synthetic handle, but decreased the efficiency of the Diels-Alder reaction and increased the overall number of synthetic steps. Nevertheless, Jung succeeded with an allene as dienophile and reported in 2001 the enantioselective formal synthesis of disidiolyde. Although, simple dienes react at low temperature, it was surprising that a more electron rich diene containing an enol ether needed higher reaction temperatures and was performed without the use of a Lewis acid.



Danishefski's 1998 total synthesis of dysidiolyde (13 steps) **Boukouvalas' 1998 total synthesis of dysidiolyde (18 steps)**



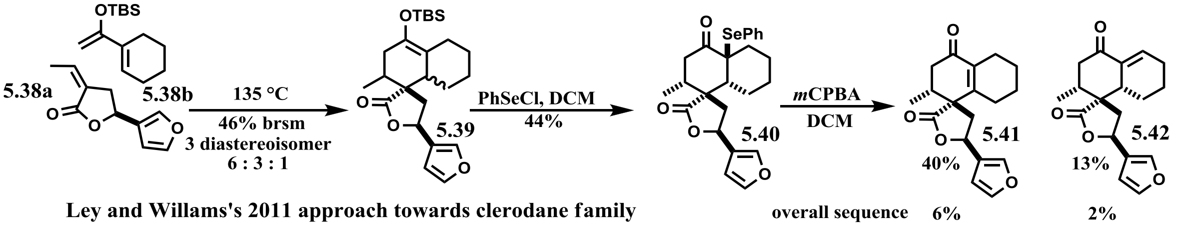
Jung's 2001 formal synthesis of dysidiolyde (23 steps) **Ley and Willams's 2011 approach towards clerodane family**

Scheme 5.05 *Examples of Diels-Alder reactions in syntheses of dysidiolide*

The major drawback of silyl enol ether dienes is their instability in Lewis acidic conditions. Hydrolysis and formation of the corresponding enone inhibited the Diels-Alder reaction.

Except for few examples, mostly developed by professor Jung, only thermal conditions had successfully been applied to sterically hindered Diels-Alder reactions of silyl enol ether dienes.[23] A recent study towards the synthesis of clerodane lactone members demonstrated the difficulties associated with this particular issue.[25] All attempts to drive the reaction forward between lactone (**5.36a**) and diene (**5.36b**) using Lewis acids failed entirely; only heating at 130 °C in a presilylated glass pressure vessel led to adduct **(5.37)** in 31% yield. Fortuitously, *cis*-decalin (**5.37**) was attained as the sole diastereomer (**Scheme 5.05**).

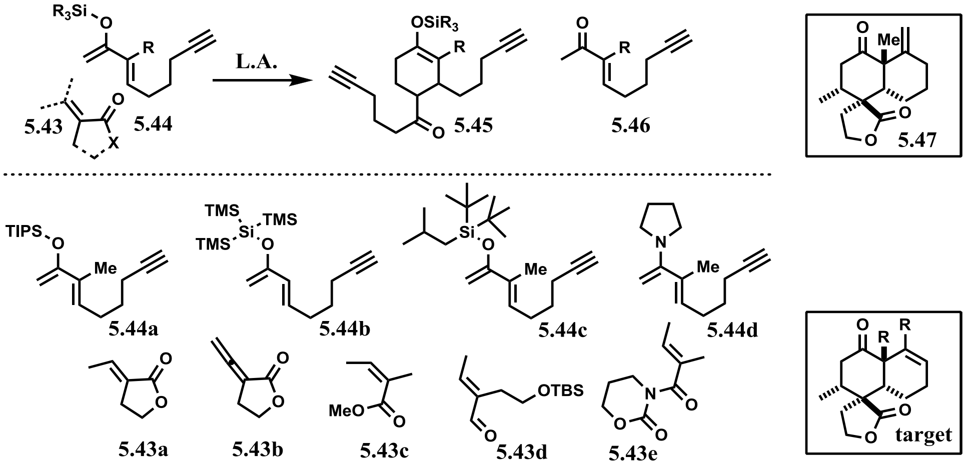
The Diels-Alder reaction between lactone (**5.38a**) and silyl enol ether diene (**5.38b**) did not offer the desired level of diasteroselectivity; cycloadduct (**5.39**) was produced in 46% yield as a mixture of 3 inseparable diastereomers in a ratio of 6: 3: 1 (**Scheme 5.06**). However, treatment of mixture (**5.39**) with phenylselenyl chloride afforded **(5.40)** as the major compound in 44% yield. Unfortunately, elimination using m-CPBA protocols gave enones (**5.41**) and (**5.42**) in 40% and 13% yields respectively. Overall, the desired advanced intermediate (**5.42**) was obtained in only 2% yield over three steps.



Scheme 5.06 *Synthesis of an advanced intermediate for cis-clerodane members containing γ-spirolactone moiety*

This last study from professor Ley and Williams demonstrated the synthetic potential as well as the major limitations encountered with this type of approach. There is little doubt that the reactivity of the diene was sufficient, but its instability limited the use of Lewis acids. Therefore, higher temperature was needed, which led to poor stereochemical control. Our hypothesis to overcome this limitation was the use of more stable silyl enol ethers or equivalent derivatives. The BIBS silyl functionality developed by Corey's group (**5.44c**) and diene enamine (**5.44d**) were two of our first targets.[26] The former had demonstrated superior stability towards acidic reaction conditions, while the second could potentially open the door towards an enantioselective variant of the reaction. However, all our efforts to synthesize these types of dienes failed.

We had then set our hopes on synthesizing the super silyl diene (**5.44B**). Super silyl is a functional silico group that was used in an impressive aldol cascade reaction by Professor Yamamoto.[27] Reports indicate that this silyl group brings outstanding diastereoselectivity and enhances the nucleophilic properties of the corresponding silyl enol ether. Disappointingly, we have not been able to generate the desired product, as the only reaction that occurred under various conditions was the hydrolysis of the silyl enol ether. In our previous studies, we had used TIPS as our standard silyl group and, therefore, we tried most reaction conditions and dienophiles with substrate (**5.44a**). Other than hydrolysis product (**5.46**), the only side-product isolated and identified was compound (**5.45**), resulting from the hydrolysis of diene (**5.44**) followed by a subsequent dimerization.



Scheme 5.07 *Resume of our unsuccessful Diels-Alder reactions*

5.6 Conclusion

In conclusion, we have developed a selective divergent synthesis of three different fused carbocycles from the same precursor (**5.04**). Moreover, we have efficiently accessed the *6-endo-dig* pathway on terminal alkynes without the formation of a vinylidene intermediate. For this purpose, new silver(I) and copper(I) catalysts were prepared and fully characterized. This work suggests that silver(I) and copper(I) catalysis can be uniquely effective to complement gold(I) catalysis and could be applied to solve selectivity problems in other catalytic reaction. In addition, these complexes provided access to interesting polycycles (**5.09e-f**), which were synthesized from a linear precursor. Our study towards the application of this methodology to the synthesis of *cis*-clerodane natural products is still under way.

Even though our initial success in the synthesis of *cis*-decalin model compounds seemed promising, two major issues appeared and still have not been fully resolved. Firstly, the Diels-Alder reaction with a tri-substituted dienophile represented a great challenge and, secondly, we did not have the right tools to achieve a selective *6-endo-dig* carbocyclization in order to access decalin frameworks with a vicinal quaternary center. Similarly, in our studies on silver(I) catalysis, the model compound closely related was found to be our only limitation in the divergent synthesis of fused carbocycles. Our initial hopes to address these two concerns relied on the use of silyl groups with unique reactivity, such as super silyl and BIBS. Even if our preliminary results were disappointing, we still believe that these two silyl group have great potential for use in Diels-Alder reactions and selective gold(I)-catalyzed reactions. The failed attempts at synthesizing model compound (**5.47**) should, in this author's opinion, be considered to be the result of a lack of time to further investigate this method rather than a discredit to the method itself.

5.7 References

1 **See** ***1.6 References 2***

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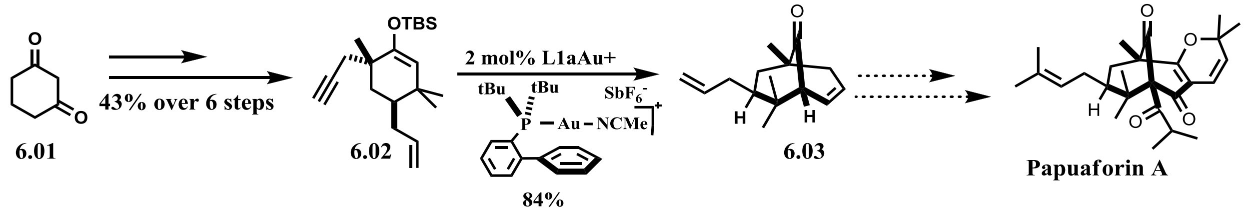
Chapter 6

General Conclusion

6.1 Summary and insight

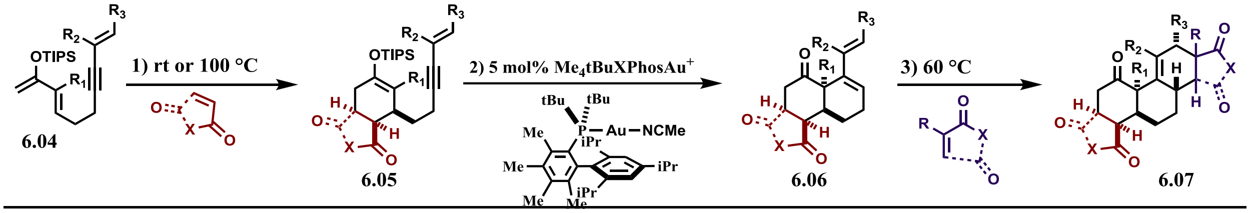
Most of my research was based on the development of new selective gold(I)-catalyzed transformations, but always related to the synthesis of complex natural products. My first project was target oriented towards the synthesis of PPAP natural products using a gold(I)-catalyzed 6-*endo-dig* carbocyclization as the key step for the formation of the bridged bicycle framework (**Scheme 6.01**). After identifying JohnPhos gold(I) complex (**L1aAu+)** as a suitable catalyst for the 6-*endo-dig* carbocyclization, a comprehensive scope was done leading to the synthesis of 15 different bicyclo[m.3.1]alkanones in addition to an advanced synthetic intermediate of Papuaforin A. The attractive feature of this method resides in its ability to construct carbon-bridged medium rings of various sizes, as well as the installation of both quaternary carbon centers adjacent to the bridgehead ketone.



Scheme 6.01 Synthesis of an advance intermediate towards the synthesis of papuaforin A

This first project revealed the importance of biphenylphosphino gold(I) catalysts, however we noticed that in contrast with palladium(0)-catalysis, no in depth study of the ligand effect has been conducted. We recognized the great opportunity to study this family of ligands in gold catalysis. In accordance with the literature, I observed a dichotomy in reactivity between these two catalysts. JohnPhos gold(I) complex (**L1aAu+**) gives moderate to good selectivity for the 6-*endo-dig* pathway, whereas IPr gold(I) complex (**L9Au+**) gives moderate to excellent selectivity for the competing 5-*exo-dig* pathway. We were rapidly excited by the synthetic opportunities that the 6-*endo-dig* pathway could offer, giving access to functionalize decalin frameworks embed of a cyclic diene moiety.

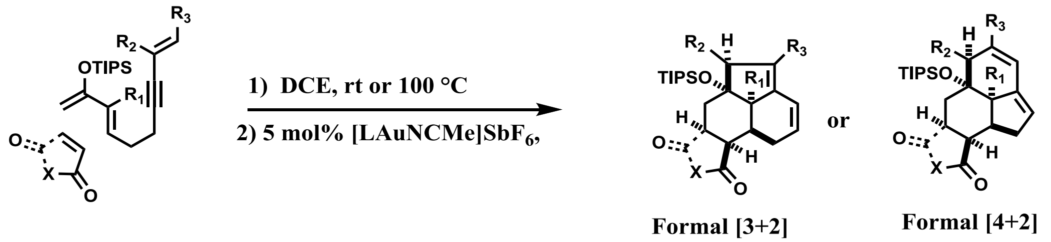
Therefore, the Diels-Alder/gold(I)-catalyzed 6-*endo-dig* carbocyclization/Diels-Alder (D.-A./ 6-*endo* Au/ D.-A.) sequence was designed in order to access polycyclic scaffolds related to diterpenes and steroids (**Scheme 6.02**).



Scheme 6.02 *Diels-Alder/gold(I)-catalyzed 6-endo-dig carbocyclization/Diels-Alder sequence*

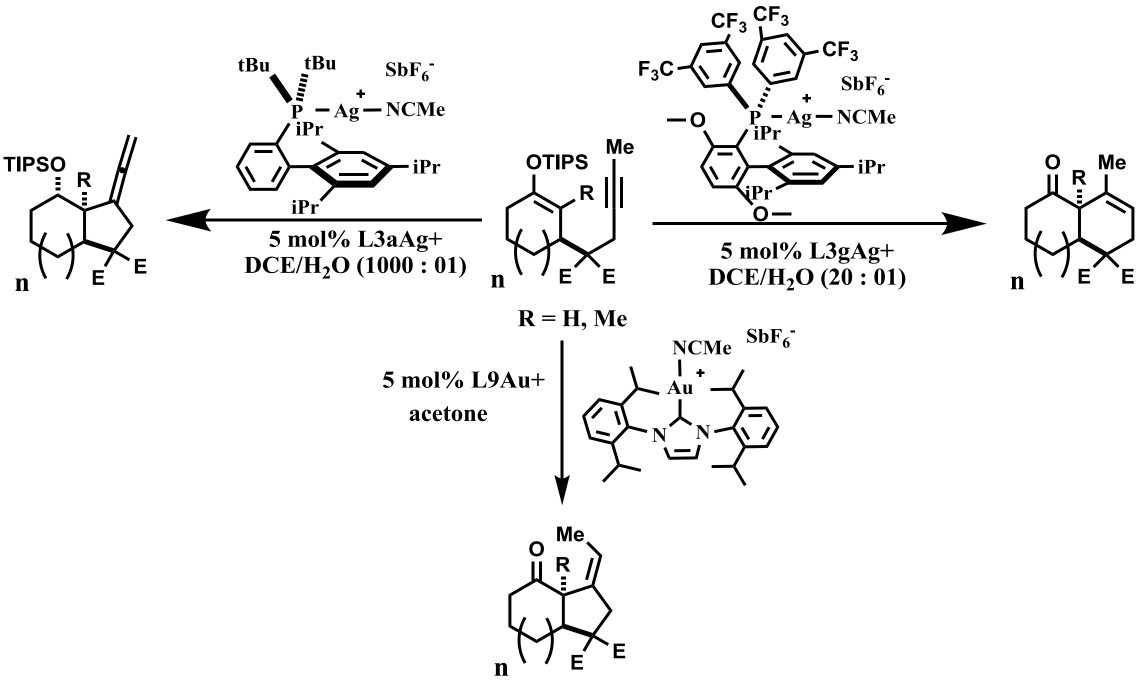
Although we already have a tendency towards the 6-*endo-dig* pathway, we did not have an acceptable level of selectivity to develop an efficient synthetic tool. After screening all the commercially available bulky biarylphosphine ligand, we identified Me_4tBuXPhos (**L8a**) as the best ligand for the gold(I)-catalyzed 6-*endo-dig* carbocyclization. The observed cyclization selectivity strongly suggests that this bulky biarylphosphine ligand has unique steric properties which influence the electronic properties of the gold(I) center. The more rigid biphenyl moiety induces a greater distortion in the linear geometry and shields a higher %VBur. I was really proud of the recognition of Professor Liming Zhang, an important player in the field of gold(I) catalysis, who ended one of his papers by "This study, as well as the work of Barriault and co-workers, suggests that cationic gold complexes based on Me_4tBuXPhos can be uniquely effective and should be included in the ligand repertoire of practitioners interested in gold catalysis."[1] This was the best part of my research; as surprising results were discovered more often than frustrating ones.

After this discovery, we explored the (D.-A./ 6-*endo* Au/ D.-A.) sequence. Despite all of our efforts to access these bicyclic dienes (**6.06**), we only obtained limited results. Although I saw a few signals of steroid-related compounds by ^{1}H-NMR in the crude reaction mixtures, I could not report an example with a reliable yield and full characterization data. The Prins type cyclization that follows the formation of the desired carbon-carbon bond limits the scope of the (D.A.-/ 6-*endo* Au/ D.-A.) sequence. While this issue is difficult to avoid, the development of selective formal [4+2] or [3+2] cycloadditions are synthetically desirable. Moreover, we took advantage of the divergence of the catalytic cycle to selectively build more complexity and diversity from a single common mechanistic intermediate.



Scheme 6.03 *Diels-Alder/ gold(I)-catalyzed formal[3+2] or [4+2] sequence*

The gold(I)-catalyzed divergent synthesis of fused carbocycles reached some limitations during our research. Regioselective control was found to be substantially more challenging with terminal alkynes, or alkynes bearing a sterically and electronically neutral methyl substituent. One of our hypotheses to improve the selectivity of the 6-*endo-dig* pathway was the geometry around the gold(I) atom. To the best of our knowledge, Me$_4$tBuXPhosAu+ (**L8aAu+**) is one of the most bent complex for monometallic gold(I) species. This issues bring us to investigate the related silver(I) and copper (I) complexes. These complexes exhibit a greater distortion in the linear geometry compare to the corresponding gold(I) complex. Furthermore, these catalysts have an embedded electron rich phosphine ligand and are still active in the electrophilic activation of alkyne.



Scheme 6.04 *Selective divergent synthesis of fused carbocycles*

Conclusion

The complementarity of these catalysts to gold(I) catalyst has allowed the development of a selective divergent synthesis of three different fused carbocycles from the same precursor. Moreover, we have efficiently accessed the *6-endo-dig* pathway on terminal alkynes without the formation of a vinylidene intermediate. This work suggests that silver(I) and copper(I) catalysis can be uniquely effective to complement gold(I) catalysis and, perhaps, could be applied to solve selectivity problems in other catalytic reactions. Disappointingly, preliminary investigations towards the application of these methodologies to the total synthesis of diverse terpenes have failed. However, as we know for academic research in organic chemistry, the journey is more important than the destination. Even though I was not successful in the synthesis of a natural product, I hope I brought new knowledge that will help others to succeed in this endeavor.

Reference 1 Wang, Y.; Ji, K.; Lan, S.; Zhang, L. *Angew. Chem. Int. Ed.* **2012**, *51,* 1915 –1918

6.2 Claims to Original Research

1- Synthesis of 15 bicyclo[m.3.1]alkanones and an advanced intermediate towards the synthesis of PPAPs natural products.

2- Development of a sensitive reaction platform for the design of new catalyst and identification of the present limitation which can be useful to further improve ligand properties.

3- Synthesis, characterization and catalytic activity evaluation of new gold(I) catalysts based on bulky biarylphosphines, in particular **Me_4tBuXPhosAu**, which possess unique steric and electronic properties

4-Development of a general 6-*endo-dig* carbocyclization with gold(I), silver(I) and copper(I) catalysis (in collaboration with Patrick Lévesque)

5- Development of a selective divergent synthesis of fused carbocycles and its application to the synthesis of three different polycyclic scaffolds related to terpenes natural product from a linear precursor in an one-pot process (collaboration with Guillaume Revol and Stéphanie Lanoix)

6-Synthesis of complex tridimensional polycyclic frameworks which are interesting from a medicinal chemistry perspective

7- Imagination of a synthetic approach based on a formal gold(I)-catalyzed cycloaddition towards the synthesis of alkaloid natural products magellanine, lycoposerramine and thiersindole A (Laboratory's work performed by Genevieve Bétournay and Phillippe McGee)

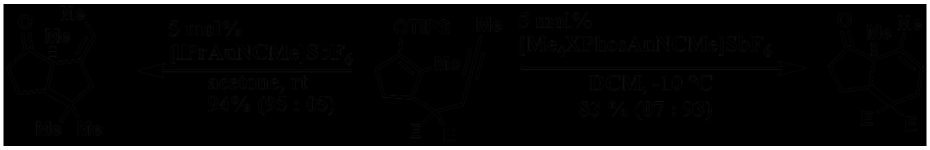
6.3 Publications from this research

Barabé, F., Levesque, P., Korbokov, I. and Barriault, L. **Merging the biarylphosphane ligand Family with gold(I) silver(I) and copper(I) catalysis**. *In preparation*

Revol, G.; Lanoix, S.; Barabé, F. and Barriault, L. **Building molecular diversity with gold(I) catalysis.** *In preparation*

Barabé, F., Levesque, P., Sow, B.,Bellavance, Bétournay G. and Barriault, L. **Gold(I)-catalyzed formation of bridged and fused carbocycles**. *Pure Appl. Chem.* **2013**, 85, 1161-1173

Barabé, F., Levesque, P., Korbokov, I. and Barriault, L. **Selective gold(I)-catalyzed *6-endo-dig* carbocyclization.** *Org. Lett.* **2011**, 13, 5540-5583.



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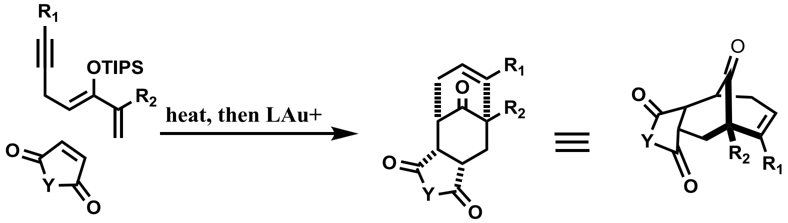

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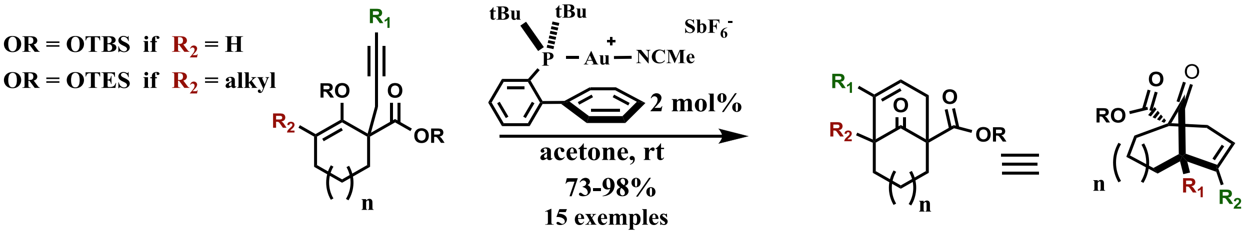


Chapter 7

Experimental

7.1 General Information

All reactions were performed under nitrogen or argon atmosphere in flame-dried glassware equipped with a magnetic stir bar and a rubber septum, unless otherwise indicated. Most solvents were freshly distilled prior to use; diethyl ether and THF over sodium and benzophenone; toluene, triethylamine, and DCM over calcium hydride. All other commercial reagents were used without further purification, unless otherwise noted. The acetonitrile[(2-biphenyl)di-*tert*-butylphosphine]gold(I) complex was purchased from Sigma-Aldrich® and kept on bench without any further precaution or made as reported in the literature[1]. Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I) and Chloro[2-dicyclohexyl(2′,4′,6′-trisopropylbiphenyl)phosphine]gold(I) were purchased from Sigma-Aldrich® but used as its acetonitrile cationic form with hexafluroantimonate as counterion..[1] The acetonitrile (2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropyl-1,1′-biphenyl)gold(I) complex was synthetized as mentioned in previous publication[2] and the ligand was purchased from Strem Chemical inc.. Silver(I) hexafluroantimonate was also purchased from Strem Chemical Inc. and tetrakis(acetonitrile)copper(I) salt) was synthesized according to the literature[3] or bought form Sigma-Aldrich®. Reactions were monitored by thin layer chromatography (TLC) analysis of aliquots using glass sheets pre-coated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). Thin layer chromatography plates were viewed under UV light and stained with phosphomolybdic acid or *p*-anisaldehyde staining solution. Column chromatographies were carried out with silica gel 60 (230-400 mesh, Merck). Preparative HPLC was performed on a waters LC 4000 system equipped with a PDA detector and a 21.2 mm - 2.5 mm reverse phase columm. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker AMX 300 MHz, Bruker AMX 400 MHz and Bruker AMX 500 MHz spectrometers. NMR samples were dissolved in chloroform-*d* (unless specified otherwise) and chemical shifts are reported in ppm from ppm relative to the residual undeuterated solvent. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dddd = doublet of doublets of doublets of doublets, br = broad signal, t = triplet, q = quartet, quint = quintet, sex = sextet, sept = septuplet, m = multiplet, or otherwise noted), coupling constant. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 75.5 MHz, 100.7 MHz, or 125.7 MHz spectrometer. NMR samples were dissolved in chloroform-*d* (unless specified otherwise) and chemical shifts are reported in ppm relative to the solvent. IR spectra were recorded with a Bomem Michaelson 100 FTIR spectrometer. HRMS were obtained on a Kratos Analytical Concept instrument (University of Ottawa Mass Spectrum Centre) using electrospray ionization (ESI+). The crystals were mounted on thin glass fibers using paraffin oil and cooled to 200.15 °K. Data were collected on a Bruker AXS SMART single crystal diffractometer equipped with a sealed Mo tube source (wavelength 0.71073 Å) APEX II CCD detector. Raw data collection and processing were performed with APEX II software package from BRUKER AXS.

References

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

2- Barabé, F.; Levesque, P.; Barriault, L. *Org. Lett.* **2010**, *13*, 5580

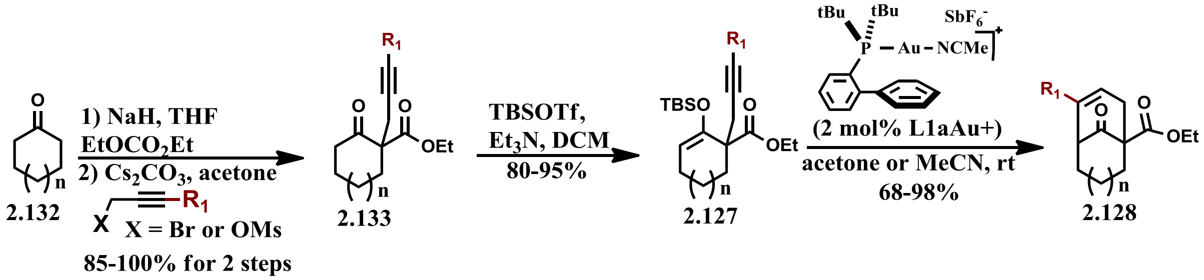
3- Pérez-Galán, P.; Delpont, N.; Herrero-Gómez, E.; Maseras, F.; Echavarren, A. M. *Chem. Eur. J.* **2010**, *16*, 5324.

Experimental Chapter 2: *PPAPs frameworks:* ***bridged bicyclic ketone***

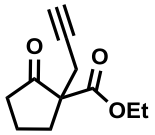
7.2 Detailed Experimental: First synthetic sequence towards bicyclo[m.3.1]alkenones

General Procedure A - Gold(I)-Catalyzed Carbocyclization

The flasks were alwayswashed in a base bath prior to use. [KOH pellets (70 g) were dissolved in *i*PrOH (1L) and distilled water (200 mL).] Flask was washed with water and acetone before starting the reaction. The flask was then charged with silyl enol ether, solvent and the gold(I) complex acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate. The mixture was stirred for 1 h to 42 h at room temperature. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 6:1)) to give cyclization product.



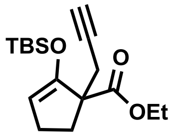
Scheme 7.01 *First synthetic sequence, R1 subtituted bridged bicyclic ketone*



2-Oxo-1-prop-2-ynylcyclopentanecarboxylic acid ethyl ester (2.133b)

The commercially available 2-cyclopentanonecarboxylic acid ethyl ester (500 mg, 3.56 mmol) was dissolved in acetone (20 mL) and cesium carbonate (2.3 g, 7.1 mmol) was added. Propargyl bromide (760 µL, 5.35 mmol) was then slowly added to the mixture at room temperature. The mixture was stirred 10 h and filtered throught a pad of Celite using AcOEt. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9 :1 to 6 :1)) to give the compound (**2.133b**) (656 mg, 95%) as a clear oil.

IR (neat, cm^{-1}) ν_{max} 3282 (m), 2980 (m), 1755 (s), 1448 (s), 1228 (s) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 4.16 (q, J =7.2 Hz, 2H), 2.71 (t, J = 2.7 Hz, 2H), 2.53-2,44 (m, 2H), 2.33-2.23 (m, 2H), 2.14-1.99 (m, 2H), 1.96 (dd, J = 2.7 Hz, 2.7 Hz, 1H), 1.24 (t, J =7.2 Hz, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 213.7 (C$_{quat}$), 170.4 (C$_{quat}$), 79.9 (C$_{quat}$), 70.7 (CH), 61.8 (CH$_2$), 58.8 (C$_{quat}$), 38.3 (CH$_2$), 32.6 (CH$_2$), 23.1 (CH$_2$), 19.7 (CH$_2$), 14.0 (CH$_3$) ; **HRMS (EI)** m/z calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0923.

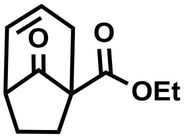


2-(*tert*-Butyldimethylsilanyloxy)-1-prop-2-ynylcyclopent-2-enecarboxylic acid ethyl ester (2.127b)

Ketoester (**2.133b**) (400 mg, 2.06 mmol) was dissolved in DCM (10 mL) and Et$_3$N (861 µL, 6.18 mmol) was added. The mixture was cooled to 0 °C and TBSOTf (982 µL, 5.15 mmol). The mixture was stirred for 8 h at 0 °C and quenched with saturated NaHCO$_3$. The aqueous layer was extracted 2 times with DCM. The organics layers was combined, dried over MgSO$_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound (**2.127b**) (525 mg, 86%) as clear oil.

IR (neat, cm^{-1}) ν_{max} 3314 (m), 2957 (m), 1732 (s), 1442 (s), 1253 (s) ; **^{1}H NMR, (400 MHz, CDCl$_3$)** δ 4.74-4.72 (m, 1H), 4.23-4.11 (m, 2H), 2,73 (dd, J = 16.8 Hz, 2.7 Hz, 1H), 2.51 (dd, J = 16.8 Hz, 2.7

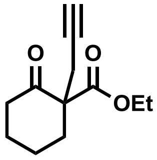
Hz, 1H), 2.39-2.24 (m, 3H), 2.11-2.02 (m, 1H), 1.88 (dd, J = 2.7 Hz, 2.7 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 174.4 (C_{quat}), 153.2 (C_{quat}), 103.2 (CH), 81.7 (C_{quat}), 69.6 (CH), 61.0 (CH_2), 58.2 (C_{quat}), 31.7 (CH_2), 26.8 (CH_2), 25.6 (CH_3x3), 24.6 (CH_2), 18.2 (C_{quat}), 14.3 (CH_3), -4.8 (CH_3), -5.0 (CH_3) ; **HRMS (EI)** m/z calcd for $C_{178}H_2O_3Si_1$ [$(M-C_5H_{10}O_2)^+$] 251.1103, found 251.1094.



8-Oxo-bicyclo[3.2.1]oct-3-ene-1-carboxylic acid ethyl ester (2.128b)

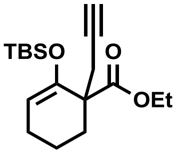
Bicycloalkanone **(2.128b)** was prepared according to the general procedure A for the gold(I)-catalyzed carbocyclization, employing silyl enol ether (**2.127b**) (80 mg, 0.26 mmol) and acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (4 mg, 0.005 mmol) in acetone (3 mL). The mixture was stirred 12h at room temperature. The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9 :1 to 4:1)) to give the compound **(2.128b)** (46 mg, 85%) as a clear oil

IR (neat, cm^{-1}) ν_{max} 2986 (m), 1733 (s), 1450 (s), 1240 (m) ; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 5.82 (tdd, J = 9.2 Hz, 6.7 Hz, 0.9 Hz, 1H), 5.60 (ddd, J = 9.2 Hz, 4.0 Hz, 2.6 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.28 (dq, J = 17.7 Hz, 2.3 Hz, 1 H), 2.71-2.60 (m, 3H), 2.20-2.03 (m, 3H), 1.28 (t, J = 7.1 Hz, 3H) ; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 211.4 (C_{quat}), 171.4 (C_{quat}), 131.9 (CH), 125.7 (CH), 61.5 (CH_2), 56.0 (C_{quat}), 46.5 (CH), 45.0 (CH_2), 30.8 (CH_2), 29.1 (CH_2), 14.3 (CH_3) **; HRMS (EI)** m/z calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0939.



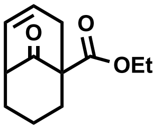
2-Oxo-1-prop-2-ynyl-cyclohexanecarboxylic acid ethyl ester (2.133a)

The commercially available 2-Cyclohexanonecarboxylic acid ethylester (4.0 g, 24 mmol) was dissolved in acetone (115 mL) and cesium carbonate (11.5 g, 35.4 mmol) was added. Propargyl bromide (5.1 mL, 47 mmol) was then slowly added to the mixture at room temperature. The mixture was stirred 10 h at room temperature and filtered through a pad of Celite using AcOEt. The solvent was evaporated off and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9 :1 to 6 :1)) to give the compound **(2.133a)** (4.9 g, 91%) as a clear oil. Spectral data is in accordance with reported data and fulll characterization is available through the literature[2].



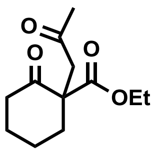
2-(*tert*-Butyldimethylsilanyloxy)-1-prop-2-ynylcyclohex-2-enecarboxylic acid ethyl ester (2.127a)

Ketoester (**2.133a**) (1.5 g, 7,7 mmol), was dissolved in DCM (25 mL) and Et_3N (861 µL, 6.18 mmol) was added. The mixture was cooled to 0 °C and TBSOTf (1.9 mL, 10.0 mmol). The mixture was stirred for 8 h at 0 °C and quenched with saturated $NaHCO_3$. The aqueous layer was extracted 2 times with DCM. The organics layers was combined, dried over $MgSO_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound (**2.127a**) (2.05 g, 91%) as a clear oil. Spectral data is in accordance with reported data and full characterization is available through the literature[3].



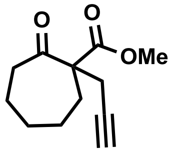
9-Oxo-bicyclo[3.3.1]non-3-ene-1-carboxylic acid ethyl ester (2.128a)

Bicycloalkanone **(2.128a)** was prepared according to the **general procedure A** for the gold(I)-catalyzed carbocyclization, employing silyl enol ether (**2.127a**) (80 mg, 0.26 mmol) and acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (4 mg, 0.005 mmol) in acetone (3 mL). The mixture was stirred 3h at room temperature. The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9 :1 to 4:1)) to give the compound **(2.128a)** (50 mg, 93%) as a white solid. Spectral data is in accordance with reported data and full characterization is available through the literature[3].



2-Oxo-1-(2-oxo-propyl)-cyclohexanecarboxylic acid ethyl ester (2.130a)

Secondary product observed during optimization of the gold(I)-catalyzed carbocyclization of (**2.127a**). **IR (neat, cm^{-1})** ν_{max} 2869 (m), 1738 (s), 1695 (s), 1459 (s), 1203 (s) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 4.13 (ddddd, J = 10.7 Hz, 7.2 Hz, 7.2 Hz, 3.6 Hz, 3.6 Hz, 2H), 2.77 (d, J = 5.1 Hz, 2H), 2.74-2.67 (m, 1H), 2.38 (dt, J = 17.0 Hz, 3.1 Hz, 1H), 2.30-2.26 (m, 1H), 2.10 (s, 3H), 1.99-1.92 (m, 1H), 1.70-1.56 (m, 4H), 1.19 (t, J = 7.2 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 207.3 (C$_{quat}$), 205.4 (C$_{quat}$), 171.9 (C$_{quat}$), 61.4 (CH$_2$), 59.2 (C$_{quat}$), 48.1 (CH$_2$), 40.5 (CH$_2$), 36.8 (CH$_2$), 30.4 (CH$_3$), 26.9 (CH$_2$), 21.9 (CH$_2$), 14.0 (CH$_3$) ; **HRMS (EI)** m/z calcd for $C_{12}H_{18}O_5$ 226.1205 found 226.1176.

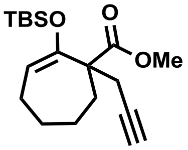


2-Oxo-1-prop-2-ynyl-cycloheptanecarboxylic acid methyl ester (2.133c)

Dimethlycarbonate (1.8 mL, 22 mmol) followed cycloheptanone (600 mg, 5.35 mmol)was slowly added to a suspension of sodium hydride (60% purity, 820 mg, 22 mmol) in THF (25 mL) at room temperature. The mixture was heated to reflux for 3h, cooled to room temperature, and slowly quenched with aqueous 2N HCl (20 mL) at 0°C. The aqueous layer was extracted with AcOEt (2 x 50 mL). The organic layers were combined and washed with brine (2 x 10 mL), dried over MgSO$_4$, filtered and concentrated to give crude yellow-orange oil which was used for the next step without further purification. The crude ketoester was dissolved in acetone (30 mL) and cesium carbonate (2.6g, 7.9 mmol) was added. Propargyl bromide (1.5 mL, 11 mmol) was then slowly added to the mixture at room temperature. The mixture was stirred 10 h at room temperature and filtered through a pad of Celite using AcOEt. The solvent was evaporated off and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 6:1)) to give the compound (**2.133c**) (1.2 g, 98%) as a clear oil.

IR (neat, cm^{-1}) ν_{max} 3322 (m), 2938 (m) 1701 (s), 1653 (s), 1437 (m), 1149 (s) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 3.72 (s, 3H), 2.91 (dd, J = 17.0 Hz, 2.7 Hz, 1H), 2.72-2.65 (m, 1H), 2.48 (dd, J = 17.0

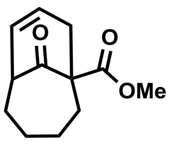
Hz, 2.7 Hz, 1H), 2.44-2.42 (m, 1H), 2.27- 2.20 (m, 1H), 2.11 (ddd, J = 15.1 Hz, 9.6 Hz, 1.7 Hz, 1H), 1.99 (dd, J = 2.7 Hz, 2.7 Hz, 1H), 1.85-1.71 (m, 2H), 1.68-1.49 (m, 3H), 1.38-1.29 (m, 1H) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 208.0(C_{quat}), 171.4 (C_{quat}), 80.2(CH), 71.1 (C_{quat}), 62.7 (C_{quat}), 52.7 (CH_3), 42.1 (CH_2), 31.5 (CH_2), 30.1 (CH_2), 25.9 (CH_2), 24.8 (CH_2), 24.5 (CH_2) ; HRMS (EI) m/z calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1095.



2-(*tert*-Butyldimethylsilanyloxy)-1-prop-2-ynylcyclohept-2-enecarboxylic acid methyl ester (2.127c)

Ketoester (**2.133c**) (300 mg, 1.44 mmol), was dissolved in DCM (10 mL) and Et_3N (723 μL, 5.19 mmol) mmol) was added. The mixture was cooled to 0 °C and TBSOTf (1.1 mL, 4.3 mmol) The mixture was stirred for 8 h at 0 °C and quenched with saturated $NaHCO_3$. The aqueous layer was extracted 2 times with DCM. The organics layers was combined, dried over $MgSO_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound (**2.127c**) (415 mg, 89%) as a white solid.

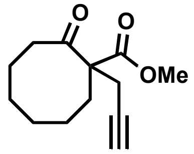
IR (neat, cm^{-1}) ν_{max} 3313 (m), 2965 (m), 2867 (m), 1740 (s), 1655 (s), 1458 (m), 1252 (s) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (t, J = 6.5 Hz, 1H), 3.69 (s, 3H), 2.83 (dd, J = 16.7 Hz, 2.7 Hz, 1H), 2.62 (dd, 16.7 Hz, 2.7 Hz, 1H), 2.13-2.03 (m, 4H), 1.99 (dd, J = 2.7 Hz, 2.7 Hz, 1H), 1.82-1.61 (m, 4H), 0.87 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 174.2 (C_{quat}), 152.2 (C_{quat}), 108.6 (CH), 81.6 (C_{quat}), 70.2 (CH), 56.3 (C_{quat}), 52.0 (CH_3), 31.0 (CH_2), 26.9 (CH_2), 25.8 (CH_3x3), 25.8 (CH_2) , 23.3 (CH_2), 22.7 (CH_2), 18.2 (C_{quat}), -4.5 (CH_3), -4.6 (CH_3) ; **HRMS (EI)** m/z calcd for $C_{18}H_{30}O_3Si_1$ [$(M-C_5H_{10}O_2)^+$] 265.1255, found 265.1268. MP = 84.5-87.0 °C.



10-Oxo-bicyclo[4.3.1]dec-7-ene-1-carboxylic acid methyl ester (2.128c)

Bicycloalkanone (**2.128c**) was prepared according to the **general procedure A** for the gold(I)-catalyzed carbocyclization, employing silyl enol ether (**2.127c**) (80 mg, 0.25 mmol) and acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (4 mg, 0.005 mmol) in acetonitrile (3 mL). The mixture was stirred 25h at room temperature. The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 4:1)) to give the compound (**2.128c**) (43 mg, 82%) as a clear oil.

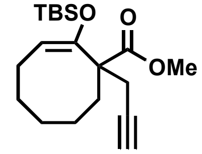
IR (neat, cm^{-1}) ν_{max} 2932 (m), 2856 (m), 1740 (s), 1293 (s) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.84 (ddt, J = 9.9 Hz, 6.1 Hz, 2.0 Hz, 1H), 5.65 (dt, J = 9.9 Hz, 2.7 Hz, 1H), 3.77 (s, 3H), 3.10-3.02 (m, 2H), 2.49 (dd, J = 14.2 Hz, 7.0 Hz, 1H), 2.37 (dd, J = 16.9 Hz, 6.0 Hz, 1H), 1.91-1.76 (m, 3H), 1.66-1.42 (m, 3H), 1.26-1.16 (m, 1H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 210.2 (C$_{quat}$), 174.2 (C$_{quat}$), 129.3 (CH), 126.0 (CH), 60.3 (C$_{quat}$), 52.4 (CH$_3$), 50,8 (CH), 37.1 (CH$_2$), 33.4 (CH$_2$), 31.6 (CH$_2$), 27.5 (CH$_2$), 26.3 (CH$_2$) **; HRMS (EI)** m/z calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1077.



2-Oxo-1-prop-2-ynylcyclooctanecarboxylic acid methyl ester (2.133d)

Dimethlycarbonate (814 μL, 9.51 mmol), followed cyclooctanone (300 mg, 2.38 mmol) was slowly added to a suspension of sodium hydride (60% purity, 370 mg, 9.52 mmol) in THF (15 mL) at room temperature. The mixture was heated to reflux for 3h, cooled to room temperature, and slowly quenched with aqueous 2N HCl (20 mL) at 0°C. The aqueous layer was extracted with AcOEt (2 x 50 mL). The organic layers were combined and washed with brine (2 x 10 mL), dried over MgSO$_4$, filtered and concentrated to give crude yellow-orange oil which was used for the next step without further purification. The crude ketoester was dissolved in acetone (25 mL) and cesium carbonate (2.3 g, 7.1 mmol) was added. Propargyl bromide (1.4 mL, 9.5 mmol) was then slowly added to the mixture at room temperature. The mixture was stirred 10 h at room temperature and filtered through a pad of Celite using AcOEt. The solvent was evaporated off and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 6:1)) to give the compound (**2.133d**) (755 mg, 88%) as a clear oil.

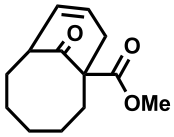
IR (neat, cm^{-1}) ν_{max} 3352 (m), 2934 (m), 2858 (s), 1740 (s), 1465 (s), 1182 (m) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 3.71 (s, 3H), 3.04 (ddd, J = 17.4 Hz, 2.7 Hz, 1.3 Hz, 1H), 2.79 (td, J = 12.1 Hz, 3.6 Hz, 1H), 2.65-2.57 (m, 1H), 2.46 (dd, J =17.4 Hz, 2.7 Hz, 1H), 2.28 (t, J = 4.3Hz, 1H), 2.25-2.19 (m, 1H), 1.99 (dd, J = 2.7 Hz, 2.7 Hz, 1H), 1.89-1.82 (m, 1H), 1.78-1.60 (m, 3H), 1.52-1.48 (m, 2H), 1.38-1.29 (m, 1H), 0.91-0.82 (m, 1H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 210.9 (C$_{quat}$), 170.8 (C$_{quat}$), 80.1 (CH), 71.1 (C$_{quat}$), 62.4 (C$_{quat}$), 53.0 (CH$_3$), 38.3 (CH$_2$), 29.6 (CH$_2$), 27.7 (CH$_2$), 25.6 (CH$_2$), 24.3 (CH$_2$), 23.2 (CH$_2$), 21.0 (CH$_2$) ; **HRMS (EI)** m/z calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1247.



2-(*tert*-Butyldimethyl-)-1-prop-2-ynylcyclooct-2-enecarboxylic acid methyl ester (2.127d)

Ketoester (**2.133d**) (400 mg, 2.06 mmol) was dissolved in DCM (10 mL) and Et$_3$N (861 µL, 6.18 mmol) was added. The mixture was cooled to 0 °C and TBSOTf (982 µL, 5.15 mmol). The mixture was stirred for 8 h at 0 °C and quenched with saturated NaHCO$_3$. The aqueous layer was extracted 2 times with DCM. The organics layers was combined, dried over MgSO$_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound (**2.127d**) (415 g, 51%) (91% brsm) as a white solid.

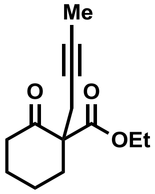
IR (neat, cm^{-1}) ν_{max} 3311 (m), 2958 (m), 1720 (s), 1367 (s), 1249 (s), 1190 (m) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.01 (t, J = 6.5 Hz, 1H), 3.69 (s, 3H), 2.82 (dd, J = 16.7 Hz, 2.7 Hz, 1H), 2.72 (dd, J = 16.7 Hz, 2.7 Hz, 1H), 2.40 (ddd, J = 15.2 Hz, 7.7 Hz, 7.7 Hz, 2H), 2.13-2.00 (m, 4H), 1.99 (dd, J =2.7 Hz, 2.7 Hz, 1H), 1.96-1.84 (m, 2H), 1.72-1.64 (m, 2H), 0.87 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 174.2 (C$_{quat}$), 151.0 (C$_{quat}$), 105.6 (CH), 81.6 (C$_{quat}$), 70.4 (CH), 56.0 (C$_{quat}$), 51.9 (CH$_3$), 33.4 (CH$_2$), 27.4 (CH$_2$), 27.2 (CH$_2$), 25.8 (CH$_3$ x3), 25.3 (CH$_2$), 23.4 (CH$_2$), 23.2 (CH$_2$), 18.2 (C$_{quat}$), -4.4 (CH$_3$), -4.5 (CH$_3$) ; **HRMS (EI)** m/z calcd for $C_{19}H_{32}O_3Si_1$ 336.21207, found 336.21023. MP = 41.8-43.2 °C.



11-Oxo-bicyclo[5.3.1]undec-8-ene-1-carboxylic acid methyl ester (2.128d)

Bicycloalkanone was prepared according to the **general procedure A** for the gold(I)-catalyzed carbocyclization, employing silyl enol ether (**2.127d**) (80 mg, 0.24 mmol), acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (4 mg, 0.004 mmol) in acetone (2 mL). The mixture was stirred 2h at room temperature. The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 4:1)) to give the compound (**2.128d**) (52 mg, 98%) as a clear oil.

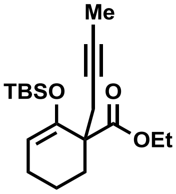
IR (neat, cm^{-1}) ν_{max} 2974 (m), 2931 (s), 1738 (s), 1444 (s), 1209 (m) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.85 (ddt, J = 10.0 Hz, 5.7 Hz, 2.2 Hz, 1H), 5.63 (dt, J = 10.0 Hz, 3.0 Hz, 1H), 3.75 (s, 3H), 3.10-3.01 (m, 1H), 3.00-2.93 (m, 1H), 2.35 (dd, J = 17.6 Hz, 5.7 Hz, 1H), 2.17-2.01 (m, 2H), 1.93-1.85 (m, 2H), 1.76-1.64 (m, 1H), 1.62-1.52 (m, 4H), 1.34-1.21 (m, 1H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 213.8 (C$_{quat}$), 173.9 (C$_{quat}$), 129.03 (CH), 125.2 (CH), 60.0 (C$_{quat}$), 52.4 (CH$_3$) , 48.1 (CH), 36.6 (CH$_2$), 34.0 (CH$_2$), 31.2 (CH$_2$), 26.9 (CH$_2$), 22.5 (CH$_2$), 21.7 (CH$_2$) ; **HRMS (EI)** m/z calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1244.



1-But-2-ynyl-2-oxo-cyclohexanecarboxylic acid ethyl ester (2.133e)

Diethlycarbonate (3.7 mL, 31 mmol) followed cyclohexanone (1.5 g, 15 mmol)was slowly added to a suspension of sodium hydride (60% purity, 1.3 g, 31 mmol) in THF (25 mL) at room temperature. The mixture was heated to reflux for 3h, cooled to room temperature, and slowly quenched with aqueous 2N HCl (20 mL) at 0°C. The aqueous layer was extracted with AcOEt (2 x 50 mL). The organic layers were combined and washed with brine (2 x 10 mL), dried over MgSO$_4$, filtered and concentrated to give crude yellow-orange oil which was used for the next step without further purification. The crude ketoester was dissolved in acetone (50 mL) and cesium carbonate (7.5 g, 23 mmol) was added. Methanesulfonic acid but-2-ynyl ester (3.3 g, 22 mmol)was then slowly added to the mixture at room temperature. The mixture was stirred 10 h at room temperature and filtered through a pad of Celite using AcOEt. The solvent was evaporated off and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 6:1)) to give the compound (**2.133e**) (3.3 g, 86%) as a clear oil.

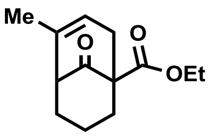
IR (neat, cm^{-1}) ν_{max} 2952 (m), 2870 (s), 1740 (s), 1717 (s), 1478 (s), 1260 (m) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 4.21 (q, J = 7.2 Hz, 2H), 2.72-2.60 (m, 2H), 2.50 (q, J = 2.6 Hz, 1H), 2.47-2.40 (m, 2H), 2.07-1.98 (m, 1H), 1.82-1.74 (m, 2H), 1.75 (t, J = 2.6 Hz, 3H), 1.70-1.54 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 206.6 (C_{quat}), 170.8 (C_{quat}), 78.8 (C_{quat}), 74.1 (C_{quat}), 61.6 (CH_2), 60.5 (C_{quat}), 41.0 (CH_2), 35.5 (CH_2), 27.5 (CH_2), 25.2 (CH_2), 22.5 (CH_2), 14.3 (CH_3), 3.7 (CH_3) **; HRMS (EI)** m/z calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1247.



2-(*tert*-Butyl-dimethyl-silanyloxy)-1-but-2-ynylcyclohex-2-enecarboxylic acid ethyl ester (2.127e)

Ketoester (**2.133e**) (250 mg, 1.13 mmol), was dissolved in DCM (7 mL) and Et_3N (392 µL, 2.81 mmol) was added. The mixture was cooled to 0 °C and TBSOTf (430 µL, 2.3 mmol) The mixture was stirred for 8 h at 0 °C and quenched with saturated $NaHCO_3$. The aqueous layer was extracted 2 times with DCM. The organics layers was combined, dried over $MgSO_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound (**2.127e**) (332 mg, 88%) as clear oil.

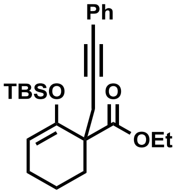
IR (neat, cm^{-1}) ν_{max} 2965 (s), 2851 (m), 1730 (s), 1453 (s), 1216 (m) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 4.86 (dq, J = 4.1 Hz, 1H), 4.13 (qd, J = 7.1 Hz, 2.5 Hz, 2H), 2.69 (dq, J = 16.5 Hz, 2.5 Hz, 1H), 2.55 (dq, J = 16.5 Hz, 2.6 Hz, 1H), 2.08-2.04 (m, 2H), 2.02-1.96 (m, 2H), 1.76 (t, J = 2.6 Hz, 3H), 1.69-1.57 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 0.88 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 174.8 (C_{quat}), 149.5 (C_{quat}), 104.1 (CH), 77.4 (C_{quat}), 76.2 (C_{quat}), 60.8 (CH_2), 50.8 (C_{quat}), 32.1 (CH_2), 25.9 (CH_2), 25.7 (CH_3x3), 24.0 (CH_2), 19.4 (CH_2), 18.3 (C_{quat}), 14.4 (CH_3), 3.7 (CH_3), -4.6 (CH_3x2) ; **HRMS (EI)** m/z calcd for $C_{19}H_{32}O_3Si_1$ 336,2121, found 336.2113.



4-Methyl-9-oxo-bicyclo[3.3.1]non-3-ene-1-carboxylic acid ethyl ester (2.128e)

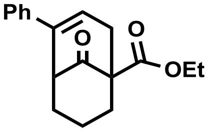
Bicycloalkanone was prepared according to the **general procedure A** for the gold(I)-catalyzed carbocyclization, employing silyl enol ether (**2.127e**) (80 mg, 0.24 mmol) acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (3.8 mg, 0.0048 mmol) in acetone (3 mL). The mixture was stirred 6h at room temperature. The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 4:1)) to give the compound (**2.128e**) (49 mg, 92%) as a clear oil.

IR (neat, cm^{-1}) ν_{max} 2933 (s), 2886 (s), 1739 (s), 1442 (s), 1275 (m) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.63 (tq, J = 3.4 Hz, 1.6 H, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3,30 (d, J = 18.7 Hz, 1H), 2.71 (br, 1H), 2.44 (ddq, J = 18.3 Hz, 3.8 Hz, 2.0 Hz, 1H), 2.38-2.29 (m, 1H), 1.99-1.82 (m, 4H), 1.68 (q, J = 2.2 Hz, 3H), 1.65-1.60 (m, 1H). 1.28 (t, J = 7.2 Hz, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 210.4 (C$_{quat}$), 172.3 (C$_{quat}$), 133.2 (C$_{quat}$), 122.4 (CH), 61.4 (CH$_2$), 57.5 (C$_{quat}$), 52.2 (CH), 39.1 (CH$_2$), 38.2 (CH$_2$), 31.4 (CH$_2$), 21.6 (CH$_3$), 17.8 (CH$_2$), 14.3(CH$_3$) ; **HRMS (EI)** m/z calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1251.



2-(*tert*-Butyldimethylsilanyloxy)-1-(3-phenyl-prop-2-ynyl)-cyclohex-2-enecarboxylic acid ethyl ester (2.127f)

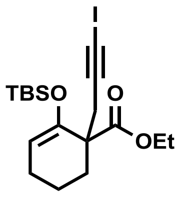
A round bottom flask was charged with copper(I) iodide (5 mg, 0.03 mmol) dichloro-bis(triphenylphosphine)palladium (II) (20 mg, 0.027 mmol) and silyl enol ether **(2.127a)** (175 mg, 444 mmol) in acetonitrile (10 mL). Phenyl iodide (91 μL, 0.81 mmol) was added and the mixture was degassed under nitrogen for 10 min. The reaction was treated with DIPEA (444 μL, 2.71 mmol) and the mixture was stirred overnight at room temperature. The solvent was evaporated off under reduce pressure and the residue was purified by flash column chromatography on silica gel (dry pack) (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound (**2.127f**) (195 mg, 90%) as a clear yellow oil. **IR (neat, cm^{-1})** ν_{max} 3048 (m), 2963 (s), 1731 (s), 1453 (s) ; **^{1}H NMR (300 MHz, CDCl$_3$)** δ 7.36-7.32 (m, 2H), 7.26-7.22 (m, 3H), 4.92 (t, J = 4.1 Hz, 1H), 4.14 (dq, J = 7.1 Hz, 1.6 Hz, 2H), 2.89 (s, 2H), 2.11-2.04 (m, 4H), 1.70-1.63 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 0.88 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 174.7 (C_{quat}), 149.0 (C_{quat}), 131.7 (CHx2), 128.2 (CHx2), 127.6 (C_{quat}), 124.2 (C_{quat}), 104.4 (CH), 87.6 (C_{quat}), 82.5 (C_{quat}), 60.9 (CH_2), 51.0 (C_{quat}), 32.5 (CH_2), 26.4 (CH_2), 25.7 (CH_3x3), 24.1 (CH_2), 19.4 (CH_2), 18.1 (C_{quat}), 14.4 (CH_3), -4.5 (CH_3), -4.7 (CH_3) ; **HRMS (EI)** m/z calcd for $C_{24}H_{34}O_3Si_1$ 398.2277, found 398.2270.



9-Oxo-4-phenyl-bicyclo[3.3.1]non-3-ene-1-carboxylic acid ethyl ester (2.128f)

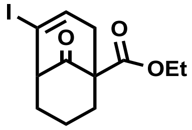
Bicycloalkanone was prepared according to the **general procedure A** for the gold(I)-catalyzed carbocyclization, employing silyl enol ether (**2.127f**) (100 mg, 0.251 mmol) , acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (4 mg, 0.005 mmol) in acetone (3 mL). The mixture was stirred 7h at room temperature. The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 4:1)) to give the compound **(2.128f)** (63 mg, 88%) as a clear oil.

IR (neat, cm^{-1}) ν_{max} 2982 (s), 2878 (m), 1734 (s), 1665 (m), 1453 (s), 1231 (m) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.32-7.26 (m, 4H), 7.24-7.19 (1H), 6.24 (dd, J = 2.7 Hz, 2.7 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.50 (dd, J = 19.6 Hz, 2.6 Hz, 1H), 3.43 (t, J = 2.7 Hz, 1H), 2.63 (dd, J = 19.5 Hz, 4.0 Hz, 1H), 2.44-2.34 (m, 1H), 2.04-1.90 (m, 4H), 1.66-1.60 (m, 1H), 1.27 (t, J =7.2 Hz, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 210.0 (C_{quat}), 172.1 (C_{quat}), 138.8 (C_{quat}), 136.4 (C_{quat}), 128.7 (CHx2), 127.7 (CH), 125.8 (CHx2), 124.6 (CH), 61.6 (CH_2), 57.7 (C_{quat}), 49.9 (CH), 39.2 (CH_2), 38.4 (CH_2), 32.6 (CH_2), 17.6 (CH_2), 14.3 (CH_3) ; **HRMS (EI)** m/z calcd for $C_{18}H_{20}O_3$ 284.1412, found 284.1411.



2-(*tert*-Butyldimethylsilanyloxy)-1-(3-iodoprop-2-ynyl)-cyclohex-2-enecarboxylic acid ethyl ester (2.127m)

To a DMF (16 mL) solution of silyl enol ether (400 mg, 1.24 mmol) was added NIS (390 mg, 1.74 mmol) and sliver nitrate (294 mg, 1.74 mmol) at 0 °C. The flask was wrapped with aluminum foil and the mixture was stirred 2h at 0°C. The reaction was quenched with saturated $Na_2S_2O_3$. The aqueous layer was extracted 3 times with hexane-AcOEt (4: 1) and the organics layers was combined, dried over $MgSO_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5) to give the compound (**2.127m**) (455 mg, 82%) as a clear oil. Spectral data is in accordance with reported data and full characterization is available through the literature[4].

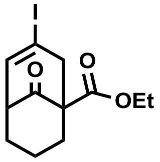


4-Iodo-9-oxo-bicyclo[3.3.1]non-3-ene-1-carboxylic acid ethyl ester (2.128m)

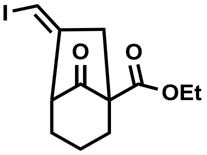
Bicycloalkanone was prepared according to the **general procedure A** for the gold(I)-catalyzed carbocyclization, employing silyl enol ether (**2.127m**) (80 mg, 0.18 mmol), acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (4 mg, 0.004 mmol) in acetone, benzene, chloroform or methanol (3 mL). The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 4:1)) to give the compounds (**2.128m)** and (**2.129m**) (52 mg, 91%) (ratio A : B = 2.1 : 1.0) in acetone, (49 mg, 88%) (ratio A : B = 2.9 : 1.0) in benzene, (47 mg, 85%) (ratio A : B = 12.5 : 1.0) in chloroform and (37 mg, 68%) (ratio A : B = 1.0 : 1.2) in methanol as a clear oil.

IR (neat, cm^{-1}) ν_{max} 2930 (s), 2857 (m), 1742 (s), 1670 (m), 1447 (s), 1326 (m) **;^{1}H NMR (300 MHz, $CDCl_3$)** δ 6.54 (t, J = 3.9 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.37 (dd, J = 18.6 Hz, 1.5 Hz, 1H), 3.20 (dd, J = 2.6 Hz, 2.6 Hz, 1H), 2.53 (dd, J = 18.6 Hz, 4.1 Hz, 1H), 2.41 (ddd, J = 13.5 Hz, 13.5 Hz, 5.0 Hz, 1H), 2.18-1.87 (m, 3H), 1.81 (ddd, J = 12.9 Hz, 3.6 Hz, 3.6 Hz, 1H), 1.75-1.64 (m, 1H), 1.29 (t, J

= 7.1 Hz, 3H) ; **^{13}C NMR (75 MHz, CDCl$_3$)** δ 206.1 (C$_{quat}$), 171.4 (C$_{quat}$), 137.7 (CH), 90.8 (C$_{quat}$), 61.8 (CH$_2$), 59.7 (CH), 57.5 (C$_{quat}$), 41.1 (CH$_2$), 39.0 (CH$_2$), 31.3 (CH$_2$), 17.2 (CH$_2$), 14.2 (CH$_3$) ; **HRMS (EI)** m/z calcd for $C_{12}H_{15}O_3I$ 334.0066, found 334.0043.



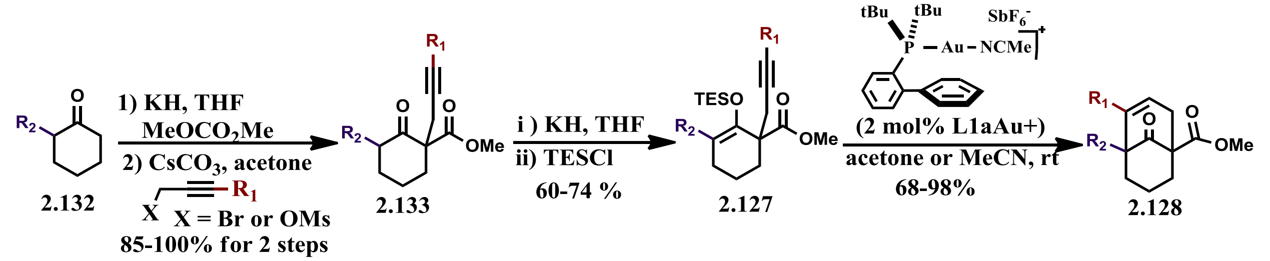
and not



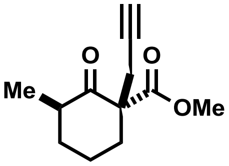
6-Iodomethylene-8-oxo-bicyclo[3.2.1]octane-1-carboxylic acid methyl ester (2.139m)

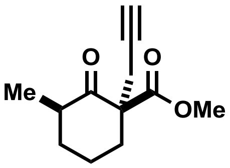
IR (neat, cm^{-1}) ν_{max} 2973 (s), 1740 (s), 1717 (s), 1670 (m), 1432 (s), 1378 (m), 1268 (m) ; **^{1}H NMR (300 MHz, CDCl$_3$)** δ 6.14 (ddd, J = 6.4 Hz, 2.2 Hz, 1.3 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.78 (d, J = 18.4 Hz, 1H), 2.93 (dd, J = 17.3 Hz, 1.2 Hz, 1H), 2.94-2.88 (m, 1H), 2.46-2.23 (m, 1H), 2.15-1.64 (m, 5H), 1.29 (t, J = 7.1 Hz, 3H) ; **^{13}C NMR (75 MHz, CDCl$_3$)** δ 207.1 (C$_{quat}$), 170.5(C$_{quat}$), 136.7 (CH), 95.1(C$_{quat}$), 61.9 (CH$_2$), 57.5 (C$_{quat}$), 51.7(CH$_2$), 51.2 (CH), 38.9 (CH$_2$), 32.9 (CH$_2$), 17.7 (CH$_2$), 14.2 (CH$_3$) ; **HRMS (EI)** m/z calcd for $C_{12}H_{15}O_3I$ 334.0066, found 333.9498.

7.3 Detailed Experimental: Second synthetic sequence towards bicyclo[m.3.1]alkenones



Scheme 7.02 *Second synthetic sequence, R1 and R2 subtituted bridged bicyclic ketone*





3-Methyl-2-oxo-1-prop-2-ynyl-cyclohexanecarboxylic acid methyl ester (2.133g)

Dimethlycarbonate (4.5 mL, 53 mmol) followed by 2-methylcyclohexanone (600 mg, 5.35 mmol) was slowly added to a suspension of potassium hydride (30% purity, 1.8 g, 13 mmol) in THF (25 mL) at room temperature. The mixture was heated to reflux for 3h, cooled to room temperature, and slowly quenched with aqueous 2N HCl (20 mL) at 0°C. The aqueous layer was extracted with AcOEt (2 x 50 mL). The organic layers were combined and washed with brine (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated to give crude yellow-orange oil which was used for the next step without further purification. The crude ketoester was dissolved in acetone (30 mL) and cesium carbonate (2.6g, 7.9 mmol) was added. Propargyl bromide (1.5 mL, 11 mmol) was then slowly added to the mixture at room temperature. The mixture was stirred 10 h at room temperature and filtered through a pad of Celite using AcOEt. The solvent was evaporated off and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 6:1)) to give the compound **(2.133g)** (2.1 g, 94%) as a clear oil. Diastereoisomeric mixture was obtained in a ratio of 1.7: 1. In a subsequent purification of an aliquot, it was possible to separate both isomers for characterization.

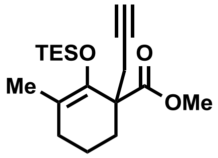
Major (2.133g):

IR (neat, cm^{-1}) ν_{max} 3287 (s), 2936 (m), 1732 (s), 1715 (m), 1451 (m), 1208 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 3.70 (s, 3H), 2.74 (dd, J = 17.6 Hz, 3.3 Hz, 1H), 2.73-2.67 (m, 1H), 2.74 (dd, J = 17.6 Hz, 3.7 Hz, 1H), 2.74-2.42 (m, 1H), 2.04-1.97 (m, 1H), 1.98 (dd, J = 2.7 Hz, 2.7 Hz, 1H), 1.85 (qt, J = 13.7 Hz, 3.8 Hz, 1H), 1.76-1.68 (m, 1H), 1.48 (td, J = 13.6 Hz, 4.3 Hz, 1H), 1.31(qd, J = 13.1 Hz, 4.0 Hz, 1H), 1.00 (d, J = 6.5 Hz, 3H) ; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 207.2 (C_{quat}), 171.0 (C_{quat}), 79.6 (CH), 71.5 (C_{quat}), 60.1 (C_{quat}), 52.7 (CH_3), 44.5 (CH), 36.6 (CH_2), 36.2 (CH_2), 25.1 (CH_2), 22.5 (CH_2), 14.7 (CH_3) ; **HRMS (EI)** m/z calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1074

Minor (2.133g):

IR (neat, cm^{-1}) ν_{max} 3279 (s), 2945 (m), 1742 (s), 1722 (m), 14651 (m), 1226 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 3.74 (s, 3H), 2.86 (dd, J = 16.8 Hz, 2.7 Hz, 1H), 2.71 (dd, J = 16.8 Hz, 3.2 Hz, 1H), 2.63-2.51 (m, 1H), 2.41-2.31 (m, 1H), 2.15 (dddd, J = 14.0 Hz, 4.7 Hz, 4.7 Hz, 2.0 Hz, 1H), 2.07-1.97 (m, 1H), 2.01 (t, dd = 2.7 Hz, 2.7 Hz, 1H), 1.90-1.68 (m, 2H).1.56-1.43 (m, 1H), 1.01 (d, J = 6.7 Hz,

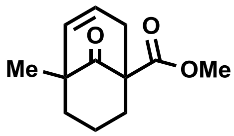
3H) ; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 209.5 (C_{quat}), 171.5 (C_{quat}), 79.1 (CH), 71.5 (C_{quat}), 60.6 (C_{quat}), 52.5 (CH_3), 42.5 (CH), 34.8 (CH_2), 32.9 (CH_2), 23.6 (CH_2), 19.8 (CH_2), 15.3 (CH_3) ; **HRMS (EI)** m/z calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1079



3-Methyl-1-prop-2-ynyl-2-triethylsilanyloxy-cyclohex-2-enecarboxylic acid methyl ester (2.127g)

Ketoester (**2.133g**) (1.7 g, 8.3 mmol) in THF (10 mL) was slowly added to a suspension of potassium hydride (30% purity, 1.6g, 12.5 mmol) in THF (40 mL) at room temperature. The mixture was stirred 1h and cooled to 0 °C. TESCl (2.5 mL, 11.6 mmol) was then added and the mixture stirred 30 min at 0 °C. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted 2 times with EtOAc. The organics layers was combined, dried over $MgSO_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound **(2.127g)** (2.1 g, 74%) as a clear oil.

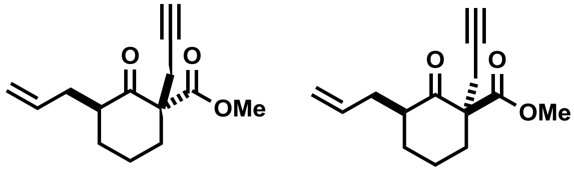
IR (neat, cm^{-1}) ν_{max} 3312 (s), 2953 (m), 1733 (s), 1376 (m), 1235 (s) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 3.68 (s, 3H), 2.81 (dd, J = 16.7 Hz, 2.7 Hz, 1H), 2.55 (dd, J = 16.7 Hz, 2.7 Hz, 1H), 2.04-97 (m, 4H), 1.95 (dd, J = 2.7 Hz, 2.7 Hz, 1H), 1.75-1.65 (m, 1H), 1.63-1.55 (m, 1H), 1.58 (s, 3H), 0.96 (t, J = 8.2 Hz, 9H), 0.66 (q, J = 8.2, 6H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 175.2 (C_{quat}), 142.3 (C_{quat}), 114.0 (C_{quat}), 81.8 (CH), 70.3 (C_{quat}), 52.1 (CH_3), 51.1 (C_{quat}), 32.9 (CH_2), 30.9 (CH_2), 25.9 (CH_2), 19.3 (CH_2), 17.8 (CH_3), 7.1 (CH_3x3), 6.0(CH_2x3) ; **HRMS (EI)** m/z calcd for $C_{18}H_{30}O_3Si_1$ 322.1964, found, 322.1981.



5-Methyl-9-oxo-bicyclo[3.3.1]non-3-ene-1-carboxylic acid methyl ester (2.128g)

Bicycloalkanone **(2.128g)** was prepared according to the **general procedure A** for the gold(I)-catalyzed carbocyclization, employing silyl enol ether **(2.127g)** (80 mg, 0.25 mmol acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (4 mg, 0.005 mmol) in acetone (3 mL). The mixture was stirred 6h at room temperature. The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 4:1)) to give the compound **(2.128g)** (48 mg, 93%) as a white powder.

IR (neat, cm^{-1}) ν_{max} 2952 (m), 1739 (s), 1695 (m), 1458 (s), 1268 (s) ; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.90 (dt, J = 9.8 Hz, 3.5 Hz, 1H), 5.28 (ddd, J = 9.9 Hz, 2.5 Hz, 1.7 Hz, 1H), 3.76 (s, 3H), 3.89 (ddd, J = 18.7 Hz, 2.4 Hz, 2.4 Hz, 1H), 2.52 (ddd, J = 18.8 Hz, 3.7 Hz, 1.6 Hz, 1H), 2.40-2.31 (m, 1H), 2.08-1.96 (m, 2H), 1.77-1.72 (m, 1H), 1.70-1.62 (m, 2H), 1.10 (s, 3H) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 211.3 (C_{quat}), 172.9 (C_{quat}), 132.2 (CH), 128.0 (CH), 58.9 (C_{quat}), 52.6 (CH_3), 47.5 (C_{quat}), 41.2 (CH_2), 39.5 (CH_2), 39.3 (CH_2), 21.7 (CH_3), 18.9 (CH_2) ; **HRMS (EI)** m/z calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1108. MP = 83.5-86.6 °C



3-Allyl-2-oxo-1-prop-2-ynylcyclohexanecarboxylic acid methyl ester (2.133h)

Dimethlycarbonate (1 mL, 15 mmol) followed by 2-allyllcyclohexanone (600 mg, 5.35 mmol) was slowly added to a suspension of potassium hydride (30% purity, 2.0 g, 15 mmol) in THF (30 mL) at room temperature. The mixture was heated to reflux for 3h, cooled to room temperature, and slowly quenched with aqueous 2N HCl (20 mL) at 0°C. The aqueous layer was extracted with AcOEt (2 x 50 mL). The organic layers were combined and washed with brine (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated to give crude yellow-orange oil which was used for the next step without further purification. The crude ketoester was dissolved in acetone (30 mL) and cesium carbonate (2.6g, 7.9 mmol) was added. Propargyl bromide (1.5 mL, 11 mmol) was then slowly added to the mixture at room temperature. The mixture was stirred 10 h at room temperature and filtered through a pad of Celite using AcOEt. The solvent was evaporated off and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 6:1)) to give the compound **(2.133h)**

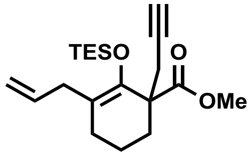
(2.1 g, 94%) as a clear oil. Diastereoisomeric mixture was obtained in a ratio of 3.1: 1. In a subsequent purification of an aliquot, it was possible to separate both isomers for characterization.

Major (2.133h):

IR (neat, cm^{-1}) ν_{max} 3286 (s), 2950 (m), 2869 (s), 1740 (m), 1701 (m), 1455 (s) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.71 (dddd, 17.3 Hz, 13.0 Hz, 7.6 Hz, 6.0 Hz, 1H), 5.00-4.94 (m, 2H), 3.71 (s, 3H), 2.74-2.68 (m, 1H), 2.73 (dd, J = 23.2 Hz, 3.2 Hz, 1H), 2.54-2.36 (m, 2H), 2.43 (dd, J = 23.2 Hz, 4.8 Hz, 1H), 2.11-2.03 (m, 1H), 1.99 (dd, J =2.7 Hz, 2.7 Hz, 1H), 1.98-1.88 (m, 1H), 1.86-1.71 (m, 2H), 1.48 (td, J = 13.5 Hz, 4.6 Hz, 1H), 1.27 (qd, J = 13.1 Hz, 4.3 Hz, 1H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 206.1 (C$_{quat}$), 170.9 (C$_{quat}$), 136.1 (CH), 116.4 (CH$_2$), 79.5 (C$_{quat}$), 71.5 (CH), 60.3 (C$_{quat}$), 52.7 (CH$_3$), 49.3 (CH), 36.2 (CH$_2$), 34.1 (CH$_2$), 33.7 (CH$_2$), 25.1 (CH$_2$), 22.4 (CH$_2$) ; **HRMS (EI)** m/z calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1236.

Minor (2.133h):

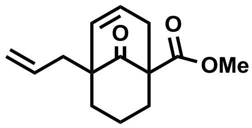
IR (neat, cm^{-1}) ν_{max} 3279 (s), 2955 (m), 2862 (s), 1742 (m), 1711 (m), 1436 (s) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.68 (dddd, J = 16.8 Hz, 10.4 Hz, 7.9 Hz, 6.0 Hz, 1H), 5.02-4.96 (m, 2H), 3.72 (s, 3H), 2.86 (dd, J = 16.5 Hz, 4.1 Hz, 1H), 2.71 (dd, J = 16.5 Hz, 2.7 Hz, 1H), 2.53-2.33 (m, 3H), 2.15-2.09 (m, 1H), 2.06-1.94 (m, 2H), 2.01 (dd, J = 2.7 Hz, 2.7 Hz, 1H), 1.88-1.80 (m, 1H), 1.78-1.67 (m, 1H), 1.54-1.44 (m, 1H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 208.3 (C$_{quat}$), 171.4 (C$_{quat}$), 135.9 (CH), 117.0 (CH$_2$), 79.1 (C$_{quat}$), 71.6 (CH), 60.8 (C$_{quat}$), 52.6 (CH$_3$), 47.4 (CH), 34.0 (CH$_2$), 32.9 (CH$_2$), 31.8 (CH$_2$), 23.7 (CH$_2$), 19.7 (CH$_2$) ; **HRMS (EI)** m/z calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1233.



3-Allyl-1-prop-2-ynyl-2-triethylsilanyloxycyclohex-2-enecarboxylic acid methyl ester (2.127h)

Ketoester (**2.133h**) (800 mg, 3.84 mmol) in THF (10 mL) was slowly added to a suspension of potassium hydride (30% purity, 775 mg, 5.76 mmol) in THF (20 mL) at room temperature. The mixture was stirred 1h and cooled to 0 °C. TESCl (1.0 mL, 9.5 mmol) was then added and the mixture stirred 30 min at 0 °C. The reaction was quenched with a saturated aqueous solution of NaHCO$_3$. The aqueous layer was extracted 2 times with EtOAc. The organics layers was combined, dried over $MgSO_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound **(2.127h)** (804 mg, 62%) as a clear oil.

IR (neat, cm^{-1}) ν_{max} 3311 (s), 2953 (m), 2877 (s), 1734 (m), 1458 (s), 1229 (s); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.70 (dddd, J =17.1 Hz, 10.1 Hz, 6.9 Hz, 6.0 Hz, 1H), 5.05 (dddd, J = 17.1 Hz, 1.9 Hz, 1.9 Hz, 1.7 Hz, 1H), 4.97 (dddd, J = 10.1 Hz, 1.7 Hz, 1.2 Hz, 1.2 Hz, 1H), 3.68 (s, 3H), 2.92 (dd, J = 14.8 Hz, 6.0 Hz, 1H), 2.77 (dd, J = 16.7 Hz, 3.0 Hz, 1H), 2.63 (dd, J =14.8 Hz, 6.9 Hz, 1H), 2.61 (dd, J = 16.7 Hz, 3.1 Hz, 1H), 2.04-1.98 (m, 4H), 1.94 (dd, J = 2.7 Hz, 2.7 Hz, 1H), 1.73-1.57 (m, 2H), 0.95 (t, J = 8.0 Hz, 9H), 0.66 (t, J = 8.0 Hz, 6H) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 175.3 (C_{quat}), 142.6 (C_{quat}), 136.3 (CH), 116.0 (C_{quat}), 115.6 (CH_2), 81.6 (C_{quat}), 70.4 (CH), 52.1 (CH_3), 51.2 (C_{quat}), 35.8 (CH_2), 33.0 (CH_2), 28.3 (CH_2), 26.0 (CH_2), 19.3 (CH_2), 7.1 (CH_3x3), 5.8 (CH_2x3) ; **HRMS (EI)** m/z calcd for $C_{20}H_{32}O_3Si_1$ 348.2121, found 348.2115.

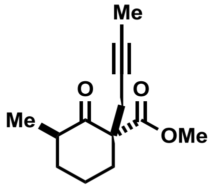


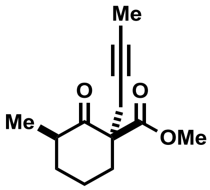
5-Allyl-9-oxo-bicyclo[3.3.1]non-3-ene-1-carboxylic acid methyl ester (2.128h)

Bicycloalkanone **(2.128h)** was prepared according to the **general procedure A** for the gold(I)-catalyzed carbocyclization, employing silyl enol ether **(2.127h)** (80 mg, 0.23 mmol), acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (3.6 mg, 0.0046 mmol) in acetone (3 mL). The mixture was stirred h at room temperature. The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 4:1)) to give the compound **(2.128h)** (50 g, 93%) as a clear oil.

IR (neat, cm^{-1}) ν_{max} 3085 (m), 2931 (s), 1739 (s), 1714 (s), 1434 (s), 1265 (m) ; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.94 (dt, J = 9.8 Hz, 3.5 Hz, 1H), 5.86-5.75 (m, 1H), 5.36 (dddd, J = 9.7 Hz, 2.4 Hz, 1.7 Hz, 1.7 Hz, 1H), 5.08-5.06 (m, 1H), 5.03 (dddd, J = 3.9 Hz, 2.5 Hz, 1.1 Hz, 1.1 Hz, 1H), 3.76 (s. 3H), 3.40 (dq, J = 18.9 Hz, 2.4 Hz, 1H), 2.51 (ddd, J = 3.7 Hz, 1.6 Hz, 1H), 2.41-2.31 (m, 2H), 2.21-2.15 (m, 1H), 2.05-1.94 (m, 2H), 1.78-1.63 (m, 3H) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 210.6 (C_{quat}), 172.8 (C_{quat}), 134.2 (CH), 129.6 (CH), 128.5 (CH), 118.1 (CH_2), 59.2 (C_{quat}), 52.6 (CH_3), 50.2 (C_{quat}), 39.5

(CH$_2$), 39.4 (CH$_2$), 39.3 (CH$_2$), 39.0 (CH$_2$), 18.65 (CH$_2$) ; **HRMS (EI)** m/z calcd for C$_{14}$H$_{18}$O$_3$ 234.1256, found 234.1252.





1-But-2-ynyl-3-methyl-2-oxo-cyclohexanecarboxylic acid methyl ester (2.133i)

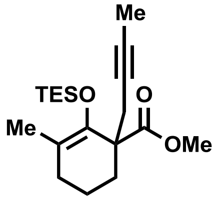
Dimethlycarbonate (4.5 mL, 53 mmol) followed by 2-methylcyclohexanone (600 mg, 5.35 mmol) was slowly added to a suspension of potassium hydride (30% purity, 1.8 g, 13 mmol) in THF (25 mL) at room temperature. The mixture was heated to reflux for 3h, cooled to room temperature, and slowly quenched with aqueous 2N HCl (20 mL) at 0°C. The aqueous layer was extracted with AcOEt (2 x 50 mL). The organic layers were combined and washed with brine (2 x 10 mL), dried over MgSO$_4$, filtered and concentrated to give crude yellow-orange oil which was used for the next step without further purification. The crude ketoester was dissolved in acetone (30 mL) and cesium carbonate (2.6g, 7.9 mmol) was added. Methanesulfonic acid but-2-ynyl ester (1.5 mL, 11 mmol) was then slowly added to the mixture at room temperature. The mixture was stirred 10 h at room temperature and filtered through a pad of Celite using AcOEt. The solvent was evaporated off and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 6:1)) to give the compound **(2.133i)** (1,8 g, 88%) as a clear oil. Diastereoisomeric mixture was obtained in a ratio of 1.4: 1. In a subsequent purification of an aliquot, it was possible to separate both isomers for characterization.

Major (2.133i):

IR (neat, cm^{-1}) ν_{max} 2934 (m), 2871 (s), 1736 (s), 1708 (s), 1453 (s), 1216 (m) ; **^{1}H NMR (300 MHz, CDCl$_3$) δ** 3.75 (s, 3H), 2.83 (dq, J = 16.8 Hz, 2.3 Hz, 1H), 2.71(dq, J = 16.8 Hz, 2.3 Hz, 1H), 2.63-2.54 (m, 1H), 2.37-2.29 (m, 1H), 2.18 (dtd, J = 16.5 Hz, 4.6 Hz, 2.4 Hz, 1H), 2.07-2.00 (m,1H), 1.5-1.78 (m, 2H), 1.75 (dd, 2.6 Hz, 2.6 Hz, 3H), 1.54-1.44 (m, 1H), 1.02 (d, J = 6.7 Hz, 3H) ; **^{13}C NMR (75 MHz, CDCl$_3$)** δ 207.7 (C$_{quat}$), 171.3 (C$_{quat}$), 78.9 (C$_{quat}$), 74.1 (C$_{quat}$), 60.5 (C$_{quat}$), 52.7 (CH), 44.6 (CH$_3$), 36.8 (CH$_2$), 36,3 (CH$_2$), 25.5 (CH$_2$), 22.7 (CH$_2$), 14.7 (CH$_3$), 3.7 (CH$_3$) ; **HRMS (EI)** m/z calcd for C$_{13}$H$_{18}$O$_3$ 222.1256, found 222.1250.

Minor (2.133i):

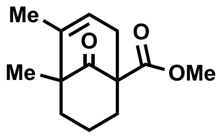
IR (neat, cm^{-1}) ν_{max} 2939 (m), 2876 (s), 1742 (s), 1713 (s), 1466 (s), 1221 (m) ; **^{1}H NMR (300 MHz, CDCl$_3$)** δ 3.72 (s, 3H), 2.76-2.69 (m, 2H), 2.50-2.40 (m, 2H), 2.02 (dddd, J = 15.6 Hz, 6.2 Hz, 3.1 Hz, 3.1 Hz, 1H), 1.89 (qt, J = 13.5 Hz, 3.8 Hz, 1H), 1.78-1.71 (m, 1H), 1.74 (t, J = 2.6 Hz, 3H), 1.46 (td, J = 13.6 Hz, 4.3 Hz, 1H), 1.33 (qd, J = 13.1 Hz, 3.9 Hz, 1H), 1.03 (d. J = 6.4 Hz, 3H) ; **^{13}C NMR (75 MHz, CDCl$_3$)** δ 210.2 (C$_{quat}$), 172.0 (C$_{quat}$), 79.0 (C$_{quat}$), 73.7 (C$_{quat}$), 61.2 (C$_{quat}$), 52.5 (CH$_3$), 42.5 (CH), 35.1 (CH$_2$), 33.0 (CH$_2$), 23.9 (CH$_2$), 20.1 (CH$_2$), 15.3 (CH$_3$), 3.7 (CH$_3$) ; **HRMS (EI)** m/z calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1265.



1-But-2-ynyl-3-methyl-2-triethylsilanyloxycyclohex-2-enecarboxylic acid methyl ester (2.127i)

Ketoester (**2.133i**) (500 mg, 2.25 mmol), in THF (7 mL) was slowly added to a suspension of potassium hydride (30% purity, 455 mg, 3.37 mmol) in THF (15 mL) at room temperature. The mixture was stirred 1h and cooled to 0 °C. TESCl (465 μL, 4.41 mmol) was then added and the mixture stirred 30 min at 0 °C. The reaction was quenched with a saturated aqueous solution of NaHCO$_3$. The aqueous layer was extracted 2 times with EtOAc. The organics layers was combined, dried over MgSO$_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound **(2.127i)** 492 mg, 65%) as a clear oil.

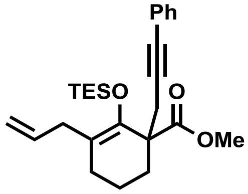
IR (neat, cm^{-1}) ν_{max} 2995 (s), 2877 (s), 1717 (s), 1436 (s), 1200 (m) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 3.68 (s, 3H), 2.81 (dd, J = 16.6 Hz, 2.7 Hz, 1H), 2.55 (dd, J = 16.6 Hz, 2.7 Hz, 1H), 2.04-1.97 (m, 4H), 1.95 (dd, J = 2.7 Hz, 2.7 Hz, 1H), 1.75-1.65 (m, 1H), 1.63-1.55 (m, 1H), 1.58 (s, 3H), 0.96 (t, J = 8.2 Hz, 9H), 0.66 (q, J = 8.2 Hz, 6H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 175.5 (C$_{quat}$), 142.8 (C$_{quat}$), 113.5 (C$_{quat}$), 77.6 (C$_{quat}$), 76.3 (C$_{quat}$), 52.0 (CH$_3$), 51.3 (C$_{quat}$), 32.8 (CH$_2$), 30.9 (CH$_2$), 26.2 (CH$_2$), 19.3 (CH$_2$), 17.9 (CH$_3$), 7.1 (CH$_3$), 6.0 (CH$_2$x3), 3.8 (CH$_3$x3) ; **HRMS (EI)** m/z calcd for $C_{19}H_{32}O_3Si_1$ 336.2121, found 336.2113.



4,5-Dimethyl-9-oxo-bicyclo[3.3.1]non-3-ene-1-carboxylic acid methyl ester (2.128i)

Bicycloalkanone **(2.128i)** was prepared according to the **general procedure A** for the gold(I)-catalyzed carbocyclization, employing silyl enol ether **(2.127i)** (80 mg, 0.24 mmol), acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (3.6 mg, 0.0047 mmol) in acetone or acetonitrile (3 mL). The mixture was stirred 20h in acetone and 40h in acetonitrile at room temperature. The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9 :1 to 4:1)) to give the compound **(2.128i)** (50 mg, 94%) in acetonitrile and (42 mg, 78%) in acetone as a clear oil.

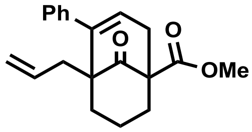
IR (neat, cm^{-1}) ν_{max} 2937 (s), 2875 (s), 1733 (s), 1450 (s), 1268 (m) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.65 (br, 1H), 3.76 (s, 3H), 3.30 (ddq, J = 18.4 Hz, 4.8 Hz, 2.4 Hz, 1H), 2.44-2.31 (m, 2H), 1.94-1.85 (m, 3H), 1.64-1.62 (m, 3H), 1.60-1.50 (m, 2H), 1.10 (s, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 211.9 (C$_{quat}$), 173.1 (C$_{quat}$), 135.9 (C$_{quat}$), 123.0 (CH), 58.0 (C$_{quat}$), 52.5 (CH$_3$), 49.9 (C$_{quat}$), 39.2 (CH$_2$), 39.1 (CH$_2$), 37.8 (CH$_2$), 19.0 (CH$_2$), 19.0 (CH$_3$), 18.3(CH$_3$) ; **HRMS (EI)** m/z calcd for $C_{13}H_{18}O_3$ 222.12559, found 222.12436.



3-Allyl-1-(3-phenylprop-2-ynyl)-2-triethylsilanyloxycyclohex-2-enecarboxylic acid methyl ester (2.127j)

A round bottom flask was charged with copper(I) iodide (5 mg, 0.03 mmol) dichloro-bis(triphenylphosphine)palladium (II) (20 mg, 0.027 mmol) and silyl enol ether **(2.127h)** (280 mg, 0.803 mmol), in acetonitrile (10 mL). Phenyl iodide (91 µL, 0.81 mmol) was added and the mixture was degassed under nitrogen for 10 min. The reaction was treated with DIPEA (444 µL, 2.71 mmol) and the mixture was stirred overnight at room temperature. The solvent was evaporated off under reduce pressure and the residue was purified by flash column chromatography on silica gel (dry pack) (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound (**2.127j**) (293 mg g, 86%) as a clear yellow oil.

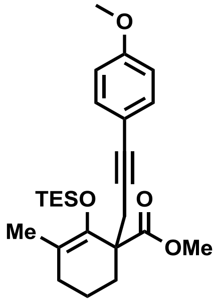
IR (neat, cm^{-1}) ν_{max} 3054 (m), 2954 (s), 2877 (s), 1735 (s), 1442 (s) ; **^{1}H NMR (300 MHz, CDCl$_3$)** δ 7.38-7.34, (m, 2H), 7.29-7.25 (m, 3H), 5.70 (dddd, J = 17.1 Hz, 10.0 Hz, 7.0 Hz, 6.0 Hz, 1H), 5.05 (dddd, J = 17.1 Hz, 2.2 Hz, 1.8 Hz, 1.8 Hz, 1H), 4.93 (dddd, J = 10.0 Hz, 2.2 Hz, 1.2 Hz, 1.2 Hz, 1H), 3.71 (s, 3H), 2.97 (dd, J = 14.7 Hz, 6.0 Hz, 1H), 2.92 (d, J = 1.4 Hz, 2H), 2.63 (dd, J = 14.7 Hz, 7.0 Hz, 1H), 2.14-1.95 (m, 4H), 1.75-1.65 (m, 2H), 0.96 (t, J = 8.2 Hz, 9H), 0.69 (q, J = 8.2 Hz, 6H) ; **^{13}C NMR (75 MHz, CDCl$_3$)** δ 175.5 (C$_{quat}$), 142.7 (C$_{quat}$), 136.3 (CH), 131.7 (CHx2), 128.2 (CHx2), 127.6 (CH), 124.2 (C$_{quat}$), 116.1 (C$_{quat}$), 115.6 (CH$_2$), 87.6 (C$_{quat}$), 82.7 (C$_{quat}$), 52.2 (CH$_3$), 51.7 (C$_{quat}$), 35.9 (CH$_2$), 33.5 (CH$_2$), 28.4 (CH$_2$), 27.0 (CH$_2$), 19.4 (CH$_2$), 7.1 (CH$_3$x3), 5.9 (CH$_2$x3) ; **HRMS (EI)** m/z calcd for $C_{26}H_{36}O_3Si_1$ 424.2433, found 424.2433.



5-Allyl-9-oxo-4-phenyl-bicyclo[3.3.1]non-3-ene-1-carboxylic acid methyl ester (2.128j)

Bicycloalkanone **(2.128j)** was prepared according to the **general procedure A** for the gold(I)-catalyzed carbocyclization, employing silyl enol ether (85 mg, 0.20mmol), acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (3 mg, 0.004 mmol) in acetone (2 mL).). The mixture was stirred 15h at room temperature. The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 4:1)) to give the compound **(2.128j)** (57 mg, 92%) as a clear oil.

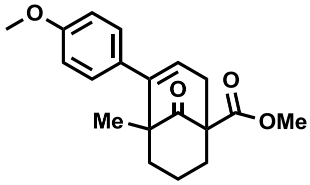
IR (neat, cm^{-1}) ν_{max} 3061 (m), 2938 (s), 2850 (s), 1737 (s), 1607 (s), 1510 (s), 1265 (m) **; ^{1}H NMR (300 MHz, CDCl$_3$)** δ 7.28-2.29 (m, 3H), 7.15-7.11 (m, 2H), 5.93 (dd, J = 3.9 Hz, 3.3 Hz, 1H), 5.63 (dddd, J = 17.1 Hz, 10.2 Hz, 7.3 Hz, 6.5 Hz, 1H), 4.79 (dddd, J = 10.2 Hz, 2.3 Hz, 1.1 Hz, 1.1 Hz, 1H), 4.61 (dddd, J = 17.1 Hz, 2.4 Hz, 1.4 Hz, 1.4 Hz, 1H), 3.72 (s, 3H), 3.48 (ddd, J = 18.9 Hz, 3.2 Hz, 1.8 Hz, 1H), 2.58 (dd, J = 18.9 Hz, 4.2 Hz, 1H), 2.45 (tdd, J = 13.4 Hz, 4.6 Hz, 1.7 Hz, 1H), 2.35-2.26 (m, 1H), 2.24-1.98 (m, 4H), 1.88-1.75 (m, 2H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 209.6 (C$_{quat}$), 172.7 (C$_{quat}$), 140.8 (C$_{quat}$), 140.5 (C$_{quat}$), 134.6 (CH), 129.0 (CH), 128.5 (CHx2), 128.0 (CHx2), 127.3 (CH), 117.5 (CH_2), 58.6 (C_{quat}), 53.7 (C_{quat}), 52.7 (CH_3), 39.3 (CH_2), 38.3 (CH_2), 38.2 (CH_2), 38.0 (CH_2), 18.9 (CH_2) ; **HRMS (EI)** m/z calcd for $C_{20}H_{22}O_3$ 310.1569, found 310.1568.



1-[3-(4-Methoxyphenyl)-prop-2-ynyl]-3-methyl-2-triethylsilanyloxycyclohex-2-enecarboxylic acid methyl ester (2.127k)

A round bottom flask was charged with copper(I) iodide (5 mg, 0.03 mmol) dichloro-bis(triphenylphosphine)palladium (II) (20 mg, 0.027 mmol) and silyl enol ether (**2.127g**) (175 mg, 444 mmol) in acetonitrile (10 mL). 4-iodoanisole (91 µL, 0.81 mmol) was added and the mixture was degassed under nitrogen for 10 min. The reaction was treated with DIPEA (444 µL, 2.71 mmol) and the mixture was stirred overnight at room temperature. The solvent was evaporated off under reduce pressure and the residue was purified by flash column chromatography on silica gel (dry pack) (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound (**2.127fk** (195 mg, 90%) as a clear yellow oil.

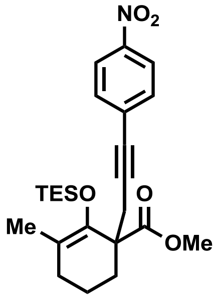
IR (neat, cm^{-1}) ν_{max} 2955 (m), 2876 (s), 1722 (s), 1607 (s), 1510 (s), 1247 (m) ;**^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.30-7.25 (dd, J = 9.5 Hz, 3.1 Hz, 2H), 6.81-6.76 (dd, J = 9.5 Hz, 3.7 Hz, 2H), 3.78 (s, 3H), 3.69 (s, 3H), 2.94 (d, J = 16.8 Hz, 1H), 2.79 (d, J = 16.8 Hz, 1H), 2.08-1.99 (m, 4H), 1.73-1.58 (m, 2H), 1.61 (s, 3H), 0.96 (t, J = 8.1 Hz, 9H), 0.69 (q, J = 8.1, 6H) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 175.6 (C_{quat}), 159.1 (C_{quat}), 142.4 (C_{quat}), 132.9 (CHx2), 116.4 (C_{quat}), 114.0 (CHx2), 113.9 (C_{quat}), 86.0 (C_{quat}), 82.3 (C_{quat}), 55.4 (CH_3), 52.0 (CH_3), 51.6 (C_{quat}), 33.3 (CH_2), 31.0 (CH_2), 26.9 (CH_2), 19.5 (CH_2), 17.9 (CH_3), 7.1 (CH_3x3), 6.0 (CH_2x3) ; **HRMS (EI)** m/z calcd for $C_{25}H_{36}O_4Si_1$ 428.23829, found 428.23856.



4-(4-Methoxy-phenyl)-5-methyl-9-oxo-bicyclo[3.3.1]non-3-ene-1-carboxylic acid methyl ester (2.128k)

Bicycloalkanone **(2.128k)** was prepared according to the **general procedure A** for the gold(I)-catalyzed carbocyclization, employing silyl enol ether (100 mg, 0.233 mmol), acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate) (3.7 mg, 0.0047 mmol) in acetone (3 mL). The mixture was stirred 15h at room temperature. The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9:1 to 4:1)) to give the compound **(2.128k)** (64 mg, 88%) as a clear oil.

IR (neat, cm^{-1}) ν_{max} 2982 (m), 2874 (s), 1735 (s), 1608 (s), 1511 (s), 1244 (m) ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.05-7.02 (dd, J = 8.7 Hz, 3.0 Hz, 2H), 6.84-6.80 (dd, J = 8.7 Hz, 3.0 Hz, 2H), 5.85 (t, J = 3.6 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.47 (ddd, J = 18.8 Hz, 3.2 Hz, 1,8 Hz, 1H), 2.59 (dd, J = 18.8 Hz, 4.0 Hz, 1H), 2.46 (tdd, J = 12.8 Hz, 4.6 Hz, 1.7 Hz, 1H), 2.25-2.16 (m, 1H), 2.15-2.03 (m, 2H), 1.78 (tt, J = 4.5 Hz, 2.1 Hz, 1H), 1.68-1.63 (m, 1H), 0.95 (s, 3H) ; **^{13}C NMR (75 MHz, CDCl$_3$)** δ 210.8 (C$_{quat}$), 172.9 (C$_{quat}$), 158.8 (C$_{quat}$), 141.0 (C$_{quat}$), 133.2 (C$_{quat}$), 129.7 (CHx2), 127.3 (CH), 113.4 (CHx2), 58.1 (C$_{quat}$), 55.4 (CH$_3$), 52.6 (CH$_3$), 50.4 (C$_{quat}$), 40.5 (CH$_2$), 39.2 (CH$_2$), 38.2 (CH$_2$), 20.1 (CH$_3$), 18.8 (CH$_2$) ; **HRMS (EI)** m/z calcd for $C_{19}H_{22}O_4$ 314.15181, found 314.14919.

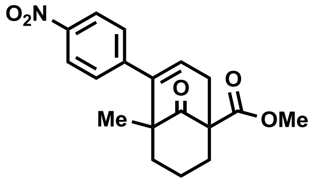


3-Methyl-1-[3-(4-nitrophenyl)-prop-2-ynyl]-2-triethylsilanyloxycyclohex-2-enecarboxylic acid methyl ester (2.127l)

A round bottom flask was charged with copper(I) iodide (40 mg, 0.21 mmol), dichloro-bis(triphenylphosphine)palladium (II) (147 mg, 0.210 mmol) and silyl enol ether **(2.127g)** (1.0 g, 3.1

mmol), in acetonitrile (40 mL). 1-Iodo-4-nitrobenzene (1.16 g, 4.66 mmol) was added and the mixture was degassed under nitrogen for 10 min. The reaction was treated with DIPEA (444 µL, 2.71 mmol) and the mixture was stirred overnight at room temperature. The solvent was evaporated off under reduce pressure and the residue was purified by flash column chromatography on silica gel (dry pack) (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound (**2.127f**) (1.05 g, 82%) as a clear yellow oil.

IR (neat, cm^{-1}) ν_{max} 3088 (m), 2896 (s), 1731 (s), 1612 (s), 1516 (s), 1338 (m) ;**^{1}H NMR (300 MHz, CDCl$_3$)** δ 8.16-8.12 (dd, J = 9.1 Hz, 2.2 Hz, 2H), 7.49-7.44 (dd, J = 9.1 Hz, 2.2 Hz, 2H), 3.71 (s, 3H), 3.00 (d, J = 15.6 Hz, 1H), 2.86 (d, J = 15.6 Hz, 1H), 2.13-1.95 (m, 4H), 1.79-1.58 (m, 2H), 1.62 (s, 3H), 0.97 (t, J = 8.0 Hz, 9H), 0.68 (q, J = 8.0 Hz, 6H) ; **^{13}C NMR (75 MHz, CDCl$_3$)** δ 175.2 (C$_{quat}$), 146.7 (C$_{quat}$), 142.1 (C$_{quat}$), 132.3 (CHx2), 131.3 (C$_{quat}$), 123.8 (CHx2), 114.3 (C$_{quat}$), 94.9 (C$_{quat}$), 81.2 (C$_{quat}$), 52.2 (CH$_3$), 51.5 (C$_{quat}$), 33.4 (CH$_2$), 30.9 (CH$_2$), 27.1 (CH$_2$), 19.4 (CH$_2$), 17.8 (CH$_3$), 7.1 (CH$_3$x3), 5.8 (CH$_2$x3) ; **HRMS (EI)** m/z calcd for $C_{24}H_{33}O_5N_1Si_1$ 443.2128, found 443.2118. MP = 70.2-74.1 °C

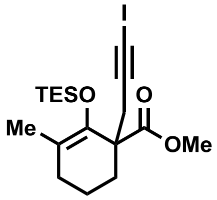


5-Methyl-4-(4-nitro-phenyl)-9-oxo-bicyclo[3.3.1]non-3-ene-1-carboxylic acid methyl ester (2.128l)

Bicycloalkanone **(2.128l)** was prepared according to the **general procedure A** for the gold(I)-catalyzed carbocyclization, employing silyl enol ether (80 mg, 0.180 mmol), acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate) (3 mg, 0.004 mmol) in acetone (3 mL). The mixture was stirred 20h at room temperature. The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9 :1 to 4:1)) to give the compound **(2.128l)** (49mg, 83%) as a white-yellow solid.

IR (neat, cm^{-1}) ν_{max} 3095 (m), 2886 (s), 1739 (s), 1612 (s), 1518 (s), 1256 (m) ; **^{1}H NMR (300 MHz, CDCl$_3$)** δ 8.18-8.14 (dd, J = 8.9 Hz, 2.4 Hz, 2H), 7.31-7.27 (dd, J = 8.9 Hz, 2.4 Hz, 2H), 5.97 (dd, J = 3.7 Hz, 3.7 Hz, 1H), 3.81 (s, 3H), 3.54 (ddd, J = 19.2 Hz, 3.7 Hz, 1.7 Hz, 1H), 2.66 (dd, J = 19.2 Hz, 3.7 Hz, 1H), 2.54-2.42 (m, 1H), 2.25-2.05 (m, 3H), 1.89-1.69 (m, 2H), 0.94 (s, 3H) ; **^{13}C NMR (75**

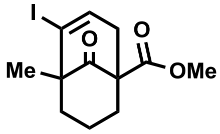
MHz, CDCl$_3$) δ 209.5 (C$_{quat}$), 172.4 (C$_{quat}$), 147.2 (C$_{quat}$), 147.2 (C$_{quat}$), 139.7 (C$_{quat}$), 129.6 (CH), 129.4 (CHx2), 123.5 (CHx2), 58.0 (C$_{quat}$), 52.8 (CH$_3$), 50.0 (C$_{quat}$), 40.6 (CH$_2$), 39.1 (CH$_2$), 38.3 (CH$_2$), 20.1 (CH$_3$), 18.9 (CH$_2$) ; **HRMS (EI)** m/z calcd for $C_{18}H_{19}O_5N_1$ 329.1263, found 329.1253.



1-(3-Iodoprop-2-ynyl)-3-methyl-2-triethylsilanyloxycyclohex-2-enecarboxylic acid methyl ester (2.127n)

To a DMF (60 mL) solution of silyl enol ether **(2.127g)** (1.1g, 3.62 mmol) was added NIS (1.1g, 4.70 mmol) and sliver nitrate (170 mg, 4.70 mmol) at 0 °C. The flask was wrapped with aluminum foil and the mixture was stirred 2h at 0°C. The reaction was quenched with saturated $Na_2S_2O_3$. The aqueous layer was extracted 3 times with hexane-AcOEt (4 : 1) and the organics layers was combined, dried over $MgSO_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound **(2.127n)** (1.3 g, 85%) as a clear oil.

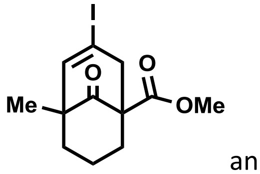
IR (neat, cm^{-1}) ν$_{max}$ 2935 (m), 2866 (s), 1745 (s), 1682 (s), 1483 (s), 1289 (m) ; **^{1}H NMR (300 MHz, CDCl$_3$)** δ 3,67 (s, 3H), 2.94 (d, J = 16.1 Hz, 1H), 2.73 (d, J = 16.1 Hz, 1H), 2.04-1.98 (m, 3H), 1.95-1.86 (m, 1H), 1.75-1.58 (m, 2H), 1.58 (s, 3H), 0.95 (t, J = 8.2 Hz, 9H), 0.64 (q, J = 8.2 Hz, 6H) ; **^{13}C NMR (75 MHz, CDCl$_3$)** δ 175.1 (C$_{quat}$), 142.0 (C$_{quat}$), 114.1 (C$_{quat}$), 91.9 (C$_{quat}$), 52.1 (CH$_3$), 51.3 (C$_{quat}$), 33.1 (CH$_2$), 30.8 (CH$_2$), 28.1 (CH$_2$), 19.3 (CH$_2$), 17.8 (CH$_3$), 7.2 (CH$_3$x3), 6.1 (CH$_2$x3), -5.3 (C$_{quat}$) ; **HRMS (EI)** m/z calcd for $C_{18}H_{29}O_3Si_1I_1$ 448.0931, found 448.0944.



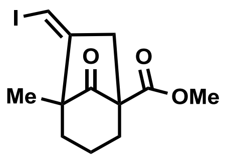
4-Iodo-5-methyl-9-oxo-bicyclo[3.3.1]non-3-ene-1-carboxylic acid methyl ester (2.128n)

Bicycloalkanone **(2.128n)** was prepared according to the **general procedure A** for the gold(I)-catalyzed carbocyclization, employing silyl enol ether (80 mg, 0.18 mmol), acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (4 mg, 0.004 mmol) in acetone, benzene, chloroform or methanol (3 mL). The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9 :1 to 4:1)) to give the compounds **(2.128n)** and **(2.128n)** (49 mg, 88%) (ratio A : B = 1.2 : 1.0) in acetone, (45 mg, 83%) (ratio A : B = 2.6 : 1.0) in benzene, (51 mg, 92%) (ratio A : B = 10.3 : 1.0) in chloroform and (40 mg, 73%) (ratio A : B = 1.0: 2.3) in methanol as a clear oil.

IR (neat, cm^{-1}) ν_{max} 2952 (m), 2874 (s), 1748 (s), 1378 (s), 1268 (s), 1106 (m) **; ^{1}H NMR (300 MHz, CDCl$_3$)** δ 6.65 (dd, J = 3.6 Hz, 3.6 Hz, 1H), 3.76 (s, 3H), 3.32 (dd, J = 18.6 Hz, 1.9 Hz, 1.9 Hz, 1H), 2.50-2.42 (m, 1H), 2.42 (dd, J = 18.7 Hz, 4.6 Hz, 1H), 2.04-1.82 (m, 3H), 1.73-1.63 (m, 1H), 1.49-1.38 (m, 1H), 1.23 (s, 3H) ; ^{13}C NMR (75 MHz, CDCl$_3$) δ 205.4 (C$_{quat}$), 172.1 (C$_{quat}$), 138.6 (CH), 103.1 (C$_{quat}$), 58.7 (C$_{quat}$), 53.7 (C$_{quat}$), 52.8 (CH$_3$), 41.1 (CH$_2$), 39.0 (CH$_2$), 38.9 (CH$_2$), 25.8 (CH$_3$), 18.8 (CH$_2$) ; **HRMS (EI)** m/z calcd for $C_{12}H_{15}O_3Si_1I_1$ 334.0066, found 334.0075.

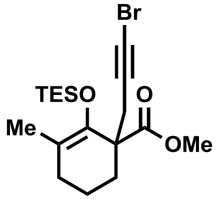


and not



6-Iodomethylene-5-methyl-8-oxo-bicyclo[3.2.1]octane-1-carboxylic acid methyl ester (2.139n)

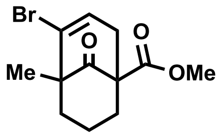
IR (neat, cm^{-1}) ν_{max} 2973 (m), 1740 (s), 1447 (s), 1268 (s), 1107 (m) ; **^{1}H NMR (300 MHz, CDCl$_3$)** δ 5.88 (dd, J = 2.1 Hz, 1.3 Hz, 1H), 3.77 (s, 3H), 2.90 (dd, J = 18.5 Hz, 1.0 Hz, 1H), 2.48-2.21 (m, 2H), 2.09-1.90 (m, 2H), 1.89-1.81 (m, 1H), 1.78-1.62 (m, 2H), 1.10 (s, 3H) ; **^{13}C NMR (75 MHz, CDCl$_3$)** δ 208.3 (C$_{quat}$), 172.0 (C$_{quat}$), 142.2 (CH), 94.3 (C$_{quat}$), 61.9 (C$_{quat}$), 53.7 (C$_{quat}$), 52.7 (CH$_3$), 51.9 (CH$_2$), 39.1 (CH$_2$), 38.9 (CH$_2$), 21.2 (CH$_3$), 19.1 (CH$_2$) ; **HRMS (EI)** m/z calcd for $C_{12}H_{15}O_3Si_1I_1$ 334.0066, found 334.0054.



1-(3-Bromoprop-2-ynyl)-3-methyl-2-triethylsilanyloxycyclohex-2-enecarboxylic acid methyl ester (2.127o)

To a DMF (60 mL) solution of silyl enol ether **(2.127g)** (1.1g, 3.62 mmol) was added NBS (1.1g, 4.70 mmol) and sliver nitrate (170 mg, 4.70 mmol) at 0 °C. The flask was wrapped with aluminum foil and the mixture was stirred 2h at 0°C. The reaction was quenched with saturated aqueous solution of $Na_2S_2O_3$. The aqueous layer was extracted 3 times with hexane-AcOEt (4 : 1) and the organics layers was combined, dried over $MgSO_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound **(2.127o)** (1.3 g, 85%) as a clear oil.

IR (neat, cm^{-1}) ν_{max} 2944 (m), 2858 (s), 1742 (s), 1667 (s), 1484 (s), 1289 (m) ; **^{1}H NMR (300 MHz, CDCl$_3$)** δ 3.67 (s, 3H), 2.80 (d, J = 16.6 Hz, 1H), 2.56 (d, J = 16.6 Hz, 1H), 2.05-1.97 (m, 3H), 1.95-1.85 (m, 1H), 1.76-1.59 (m, 2H), 1.58 (s, 3H), 0.95 (t, J = 8.5 Hz, 9H), 0.65 (q, J = 8.5 Hz, 6H) ; **^{13}C NMR (75 MHz, CDCl$_3$)** δ 175.1 (C_{quat}), 142.1 (C_{quat}), 114.0 (C_{quat}), 77.7 (C_{quat}), 52.1 (CH_3), 51.1 (C_{quat}), 39.5 (C_{quat}), 33.0 (CH_2), 30.7 (CH_2), 27.0 (CH_2), 19.2 (CH_2), 17.6 (CH_3), 6.9 (CH_2x3), 5.9 (CH_3x3) ; **HRMS (EI)** m/z calcd for $C_{18}H_{29}O_3Si_1Br_1$ 400.10693, found 400.10653.

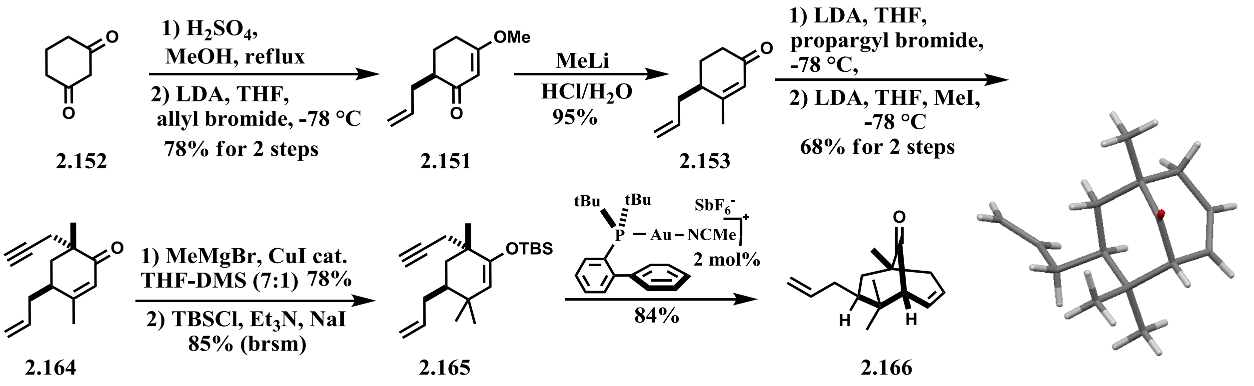


4-Bromo-5-methyl-9-oxobicyclo[3.3.1]non-3-ene-1-carboxylic acid methyl ester (2.128o)

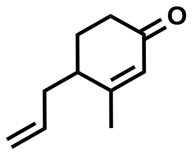
Bicycloalkanone **(2.128o)** was prepared according to **the general procedure A** for the gold(I)-catalyzed carbocyclization, employing silyl enol ether (80 mg, 0.18 mmol), acetonitrile[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (4 mg, 0.004 mmol) in acetone (3 mL). The residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (9 :1 to 4:1)) to give the compounds **(2.128o)** (52 mg, 93%) as a clear oil.

IR (neat, cm^{-1}) ν_{max} 2945 (m), 2862 (s), 1741 (s), 1363 (s), 1271 (s), 1143 (m) ; **^{1}H NMR (300 MHz, CDCl$_3$)** δ 6.33 (dd, J = 4.8 Hz, 3.2 Hz, 1H), 3.76 (s, 3H), 3.28 (ddd, J = 18.5 Hz, 3.0 Hz, 1.8 Hz, 1H), 2.49-2,39 (m, 1H), 2.40 (dd, J = 18.5 Hz, 4.7 Hz, 1H), 2.04-185 (m, 3H), 1.75-1.65 (m, 1H), 1.59-1.46 (m, 1H), 1.25 (s, 3H) ; **^{13}C NMR (75 MHz, CDCl$_3$)** δ 206.5 (C$_{quat}$), 172.0 (C$_{quat}$), 129.9 (CH), 124.0 (C$_{quat}$), 58.1 (C$_{quat}$), 53.4 (C$_{quat}$), 52.7 (CH$_3$), 38.9 (CH$_2$), 38.8 (CH$_2$), 38.0 (CH$_2$), 21.6 (CH$_3$), 18.8 (CH$_2$) ; **HRMS (EI)** m/z calcd for $C_{12}H_{15}O_3Br_1$ 286.02046, found 286.01939.

7.4 Detailed Experimental: Synthetic sequence of an advance bridged bicyclic intermediate towards the synthesis of papuaforin A

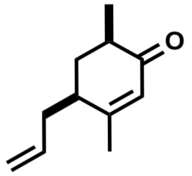


Scheme 7.03 *Successful sequence towards the synthesis of an advance bicyclic intermediate*



4-Allyl-3-methylcyclohex-2-enone (2.152)

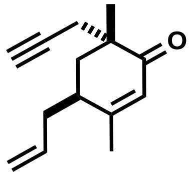
A solution of methyllithium (1.0 M in hexanes, 139.5 mL) was added dropwise to a solution of 6-allyl-3-methoxycyclohex-2-enone (19.31 g, 116.2 mmol) in dry ether at −78 °C for 30 min. The mixture was then stirred at rt for 1 h. An aqueous solution of 1 N HCl was added. After stirring for 1 h at rt, water was added. The aqueous layer was extracted with ethyl acetate (3x), and the combined organic phases were dried over anhydrous magnesium sulphate, filtered and concentrated. The crude oil was distilled under reduced pressure and purified by chromatography (10% EtOAc:hexanes) to give 14.48 g (83%) of **(2.133)** as a clear yellow oil. Spectral data is in accordance with reported data and full characterization is available through the literature[5].



4-Allyl-3,6-dimethylcyclohex-2-enone (2.164a)

A solution of *n*-BuLi (1.6 M in hexanes, 21.8 mL, 34.95 mmol) was added slowly to diisopropylamine (5.17 mL, 36.61 mmol) in THF(150 mL) at −78 °C for 45 min. 4-Allyl-3-methylcyclohex-2-enone (**8**) (5 g, 33.28 mmol) was added at −78 °C for 60 min and then iodomethane (2.49 mL, 39.94 mmol). The mixture was stirred at rt for 3 h. An aqueous saturated solution of NH_4Cl was added and the aqueous layers were extracted with ethyl acetate (3x). The combined organic phases were dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated. The crude residue was purified by flash chromatography (10% EtOAc:hexanes) to give 4.92 g (90%) of a yellow-orange oil of 4-allyl-3,6-dimethylcyclohex-2-enone **(2.164a).**

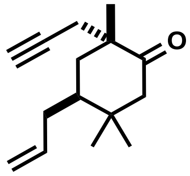
IR (neat, cm-1) vmax: 3077, 2964, 2930, 2872, 1673, 1639, 1443, 1378; **^{1}H NMR, (400 MHz, $CDCl_3$)** δ 5.81 (m, 1H), 5.79(s, 1H), 5.11(m,2H), 2.43 (m,2H), 2.27 (m,2H), 1.99 (ddd, *J* = 13.5 Hz, 4.8 Hz, 2.8 Hz, 1H), 1.95(s, 3H), 1.76(m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR (400 MHz, $CDCl_3$)** δ 201.9 (C_{quat}), 164.0 (C_{quat}), 136.5(CH), 126.4 (CH), 117.1 (CH_2), 39.2 (CH), 35.9 (CH), 35.6 (CH_2), 34.5 (CH_2), 22.9 (CH_3), 15.4 (CH_3); **HRMS (EI)** *m/z* calcd for C11H16O [M+] 164.1201, found: 164.1205.



4-Allyl-3,6-dimethyl-6-(prop-2-ynyl)cyclohex-2-enone (2.164)

A solution of *n*-BuLi (1.6 M in hexanes, 1.59 mL, 2.55 mmol) was added slowly to a solution of diisopropylamine (0.38 mL, 2.67 mmol) in THF (15 mL) at −78 °C for 45 min. 4-Allyl-3,6-dimethylcyclohex-2-enone (0.4 g, 2.44 mmol) was added at −78 °C. After stirring for 60 min, propargyl bromide (0.33 mL, 2.92 mmol) was added and the mixture was stirred at rt for 3 h. The resulting mixture was quenched with a saturated solution of NH4Cl. The aqueous layer was extracted with ethyl acetate (3x). The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was purified by chromatography (10% EtOAc:hexanes) to give (**2.164**) 0.31 g (62%) as a yellow-orange oil.

IR (neat, cm^{-1}) νmax 3305, 3077, 2976, 2930, 1674; **^{1}H NMR, (400 MHz, CDCl$_3$)** δ 5.78 (s,1H), 5.69 (m,1H), 5.10 (m,2H), 2.49 (m,2H), 2.35 (m, 1H), 2.15 (m,3H), 2.01 (t, *J* = 2.6 Hz, 1H), 1.93 (s, 3H), 1.57 (dd, *J* = 13.8, 10.3 Hz, 1H), 1.16 (s, 3H); **^{13}C NMR (400 MHz, CDCl$_3$)** δ 202.6 (C$_{quat}$), 162.9 (C$_{quat}$), 135.3 (CH), 126.5 (CH), 118.1 (CH$_2$), 80.5 (C$_{quat}$), 71.4 (CH), 43.9 (C), 38.5 (CH$_2$), 36.9 (CH), 36.7 (CH$_2$), 26.8 (CH$_2$), 22.3 (CH$_3$*2); **HRMS (EI)** *m/z* calcd for C14H18O [M+] 202.1358, found: 202.1339.

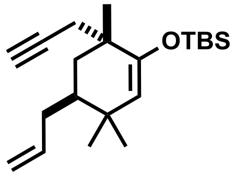


4-Allyl-2,5,5-trimethyl-2-(prop-2-ynyl)cyclohexanone (2.165a)

(Gabriel Bellavance Coop works)

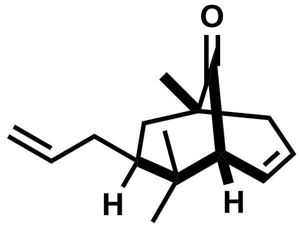
To a solution of CuI (63 mg, 0.33 mmol) and **9** (306.7 mg, 1.52 mmol) in THF (15 mL) and Me2S (1.5 mL) at 0 °C was slowly added a solution of MeMgBr (1.11 mL, 3.0 M in Et2O, 3.33 mmol) over 1 h. The mixture was then stirred for 1 h at 0 °C. An aqueous saturated solution of NH4Cl was added. The mixture was extracted with Et2O (3x). The organic phase was dried over MgSO4 and concentrated in vacuo. The residue was purified by column chromatography (10% EtOAc:hexanes) to provide the desired ketone **(2.132a)** (175.9 mg, 53%) as a dark orange oil (mixture of two conformers).

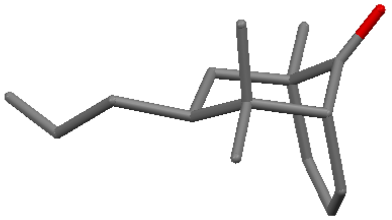
IR (neat, cm-1) νmax 3310, 3076, 2965, 2931, 2871, 2124, 1716, 1640, 1436; **^{1}H NMR, (400 MHz, CDCl$_3$)** δ 5.76 (m, 1H), 5.02 (m, 2H), 2.49 (0.5H), 2.45 (m, 1H), 2.37 (m, 2H), 2.33 (m, 0.5H), 2.00 (m, 2.5), 1.70 (m, 2.5 H), 1.26 (t, 1H), 1.09 (s,3H), 1.04 (s, 3H), 0.96 (m, 1H), 0.73 (m, 3H); **^{13}C NMR (400 MHz, CDCl$_3$)** δ 213.2 (C$_{quat}$), 137.6 (CH), 116.3 (CH$_2$), 79.5 (C), 71.5 (CH), 52.9 (CH$_2$), 48.0 (C$_{quat}$), 41.5 (CH), 40.0 (CH$_2$), 39.3 (C$_{quat}$), 34.2 (CH$_2$), 29.8 (CH$_3$), 27.8 (CH$_2$), 22.2 (CH$_3$), 20.1 (CH$_3$); **HRMS (EI)** *m/z* calcd for C15H22O [M+] 218.1671, found: 218.1659.

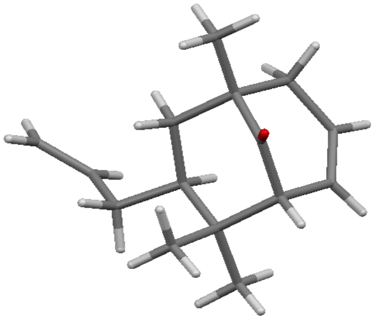


(4-Allyl-3,3,6-trimethyl-6-(prop-2-ynyl)cyclohex-1-enyloxy)(*tert*-butyl)dimethylsilane (2.165) (Gabriel Bellavance Coop works)

4-Allyl-2,5,5-trimethyl-2-(prop-2-ynyl)cyclohexanone (300 mg, 1.37 mmol) was dissolved in acetonitrile (30 mL), and Et3N (0.383 mL, 2.74 mmol) was added. Then flame-dried NaI (0.309 g, 2.04 mmol) and TBSCl (310 mg, 2.04 mmol) were added. The reaction mixture was allowed to reflux overnight and was then quenched with NaHCO3 saturated solution, and the aqueous phase was extracted with DCM (3x). The organic phases were then combined and concentrated. The resulting mixture was filtered through a small silica pad and washed with solution of 7% EtOAc in hexanes and concentrated again. The crude enol ether **(2.132)** (209 mg, 46%) was then directly used for the next reaction.







7-Allyl-5,8,8-trimethylbicyclo[3.3.1]non-2-en-9-one (2.166)

A solution of silyl enol ether **10** (20 mg, 0.060 mmol) and (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) (0.92 mg, 0.0012 mmol) in DCM (1 mL) was stirred for 6 h at rt. The solvent was evaporated and the residue was purified by flash column chromatography on silica (10% EtOAc:hexanes) to give 88% of **(2.131b)** as a white solid.

IR (neat, cm^{-1}) vmax 3081, 3039, 2967, 2921, 1709; **^{1}H NMR, (400 MHz, CDCl3)** δ 5.82 (m, 1H), 5.76 (m, 1H), 5.63 (dddd, *J* = 9.5, 6, 1.9 Hz, 1.9 Hz, 1H), 5.03 (m, 1H), 2.41 (m, 3H), 2.25 (m, 1H), 2.03 (m, 1H), 1.82 (dd, *J* = 13.9 Hz, 4.5 Hz, 1H), 1.59 (ddd, *J* = 13.7, 10.8, 8.6 Hz, 2H), 1.28 (m, 4H), 1.02 (s, 3H), 0.99 (s, 3H), 0.79 (s, 3H); **^{13}C NMR (400 MHz, CDCl3)** δ 216.50 (C_{quat}), 138.03 (CH), 129.80 (CH), 126.55 (CH), 115.96 (CH_2), 60.27 (CH), 45.96 (CH_2), 45.61 (CH_2), 42.35 (C_{quat}), 38.09 (CH), 34.09 (C_{quat}), 29.71 (CH_2), 26.09 (CH_3), 23.50 (CH_3), 20.79 (CH_3); **HRMS (EI)** *m/z* calcd for C15H22O [M+] 218.1671, found: 218.1652.

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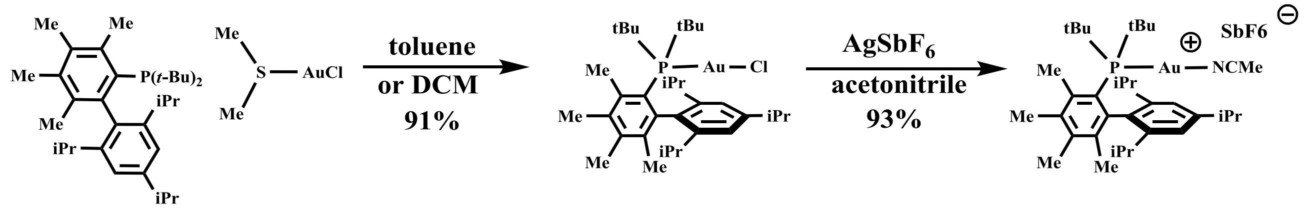
Experimental Chapter 3 and 5: *Synthesis of Gold(I), Silver(I) and Copper(I) Complexes*

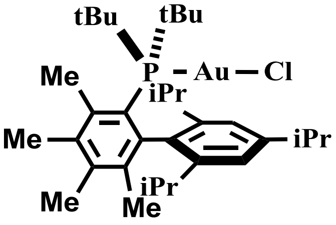
7.5 Detailed Experimental: Synthetic sequence towards cationic gold(I), silver(I) and copper(I) catalyst

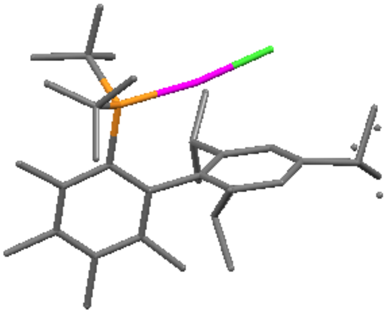
General procedure B: Synthesis of Au(I) complexes

To suspension of a phosphine (0.208 mmol) in DCM (2 mL) was added chloro(dimethylsulfide)gold(I) (61 mg, 0.208 mmol). The mixture was stirred for 4h at room temperature. The solvent was evaporated off under reduced pressure and the residue was triturated with pentane to give **L**AuCl (80-90%) as a grey powder.



Scheme 7.04 *Prepration of cationic biphenylphosphine gold(I) complexes, eg. Me$_4$tBuXPhosAu$^+$*

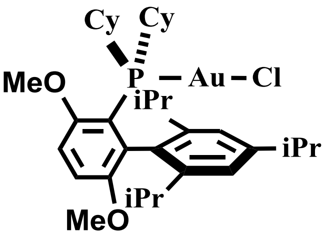


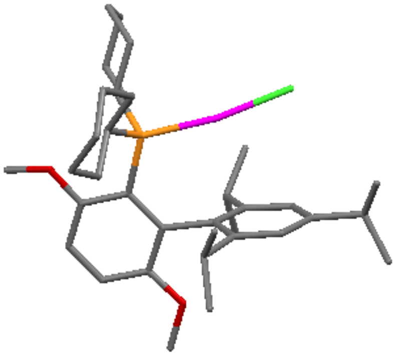


L8aAuCl (Me$_4$XPhosAuCl)

Prepared according to **the general procedure B** in 83% yield as a grey powder. (When the chloride gold(I) salt is mix with the silver salt, the solution turn bright purple and the intensity decrease after) **^{1}H NMR (400 MHz, C$_6$D$_6$)** δ 7.37 (s, 2H), 3.21 (sept, J =6.9 Hz, 1H), 2.57 (sept, J = 6.7 Hz, 2H), 2.16 (s, 3H), 189 (s, 3H), 1.85 (s, 3H), 1.64 (d , J = 6.9 Hz, 6H), 1.60 (s, 3H), 1.52 (d, J= 6.7 Hz, 6H), 1.31 (s, 9H), 1,28 (s, 9H), 0.98 (d, J = 6.7 Hz, 6H) ;**^{13}C NMR (100 MHz, C$_6$D$_6$)** δ 151.0 (C$_{quat}$), 146.9

(C_{quat}), 146.6 (C_{quat}), 146.0 (C_{quat}), 140.2 (C_{quat}) (d, J_{C-P} = 2.6 Hz),, 138.3 (C_{quat}) (d, J_{C-P} = 3.3 Hz), 138.2 (C_{quat}), 137.8 (C_{quat}) (d, J_{C-P} = 9.2 Hz), 135.9 (C_{quat}) (d, J_{C-P} = 7.0 Hz),, 129.1 (C_{quat}), 128.8 (CH), 123.3 (CH), 41.5 (C_{quat}x2) (d, J_{C-P} = 20.2 Hz),, 35.0 (CH), 33.3 (CH_3x3) (d, J_{C-P} = 8.4 Hz), 31.2 (CHx2), 27.9 (CH_3), 27.9 (CH_3), 25.4 (CH_3x3), (d, J_{C-P} = 7.7 Hz) 25.1 (CH_3x2), 22.6 (CH_3), 22.6 (CH_3), 17.6 (CH_3x2), 17.1 (CH_3x2) ; **^{31}P NMR (162 MHz, C_6D_6)** δ 76.51; **HRMS (EI)** m/z calcd for $C_{33}H_{54}PAuCl$ [$(M-Cl)^+$] = 677.3550, found 6755.3548

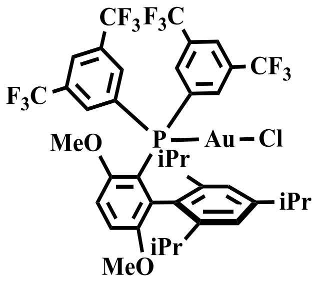


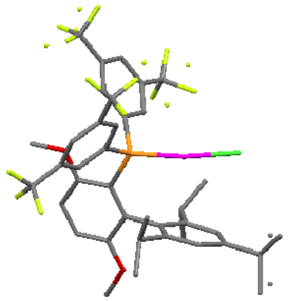


L3cAuCl (BrettPhosAuCl)

Prepared according to the **general procedure B** in 78% yield as a white powder.

^{1}H NMR (400 MHz, C_6D_6) δ 7.44 (s, 2H), 6.47 (d, J = 9.0 Hz, 1H), 6.32 (dd, J = 9.0 Hz, 3.4 Hz, 1H), 3.23 (sept, J = 7.0 Hz, 1H), 3.18 (s, 3H), 2.94 (s, 3H), 2.58 (sept, J = 6.8 Hz, 2H), 2.47 (qdd, J = 12.3 Hz, 2.8 Hz, 2.8 Hz, 2H), 2.11 (s, 1H), 1.96-1.87 (m, 2H), 1.77-1.44 (m, 10H), 1.56 (d, J = 6.9 Hz, 12H), 1.41-1.27 (m, 2H), 1.14 (d, J = 6.8 Hz, 6H), 1.10-0.99 (m, 5H); **^{13}C NMR (75 MHz, C_6D_6)** δ 155.6 (C_{quat}), 154.0 (C_{quat}) (d, J_{C-P} = 11.4 Hz), 151.1 (C_{quat}), 146.5 (C_{quat}), 139.5 (C_{quat}) (d, J_{C-P} = 14.7 Hz), 131.6 (C_{quat}) (d, J_{C-P} = 7.4 Hz), 128.9 (CH), 122.9 (CH), 119.1 (C_{quat}), 118.6 (C_{quat}), 113.9 (CH) (d, J = 2.2 Hz), 110.4 (CH) (d, J = 5.5 Hz), 55.5 (CH_3), 54.6 (CH_3), 39.6 (CHx2) (d, J_{C-P} =34.5 Hz), 35.3 (CHx2), 35.0 (CH_2x2), 34.9 (CH_2x2), 31.6 (CH), 30.6 (CH_2), 28.0 (CH_2x2) (d, J_{C-P} = 12.8 Hz), 27.4 (CH_2x2) (d, J_{C-P} = 16.1 Hz), 26.3 (CH_2), 25.9 (CH_3x2), 25.2 (CH_3x2), 24.8 (CH_3x2); **^{31}P NMR (121 MHz, C_6D_6)** δ 40.43; **HRMS (EI)** m/z calcd for $C_{35}H_{53}AuClO_2$ P [$(M-Cl)^+$] 733.3449, found 733.3512.

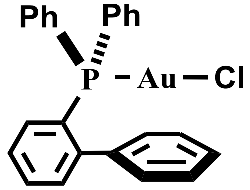




L3gAuCl (JackiePhosAuCl)

Prepared according to the **general procedure B** in 89% yield as a white powder.

^{1}H NMR (300 MHz, C_6D_6) δ 7.65 (d, J = 11.3 Hz, 4H), 7.65 (s, 2H), 7.38 (s, 2H), 6.44 (d, J = 6.4 Hz, 1H), 6.11 (dd, J = 9.1 Hz, 4.5 Hz, 1H), 3.12 (sept, J = 6.9 Hz, 1H), 2.90 (s, 3H), 2.64 (s, 3H), 2.56 (dt, J = 13.6 Hz, 6.7 Hz, 2H), 1.48 (d, J = 6.9 Hz, 6H), 1.32 (d, J = 7.0 Hz, 6H), 1.14 (d, J = 6.7 Hz, 6H); **^{13}C NMR (75 MHz, C_6D_6)** δ 154,5 (C_{quat}) , 153,9 (C_{quat}) (d, J_{C-P} = 14.3 Hz), 151.8 (C_{quat}), 146.3 (C_{quat}), 139.3 (C_{quat}), 139.0 (C_{quat}), 134.7 (C_{quat}), 133.9 (C_{quat}), 133.0-132.9 (C_{quat}) (m), 132.8-132.7 (C_{quat}) (m), 132.6 (C_{quat}), 132.9 (CH), 132.6 (CH), 132.4 (C_{quat}), 132.1 (C_{quat}), 131.8 (C_{quat}) (d, J_{C-P} = 11.5 Hz), 130.1 (C_{quat}) (d, J_{C-P} = 9.0 Hz), 128.3 (CHx4), 125.0 (C_{quat}), 124.7-124.6 (C_{quat}) (m), 124.6 (CH), 123.1 (CH), 121.4 (C_{quat}), 117.0 (CH), 111.3 (CH) (d, J_{C-P} = 5.5 Hz), 54.7 (CH_3), 54.2 (CH_3), 34.9 (CH), 32.1 (CHx2), 25.1 (CH_3x2), 24.6 (CH_3x2), 23.8 (CH_3x2) ; **^{31}P NMR (121 MHz, C_6D_6)** δ 16.00; **HRMS (EI)** m/z calcd for $C_{39}H_{37}O_2PF_{12}AuCl$ 1028.1692, found 1028.1646.

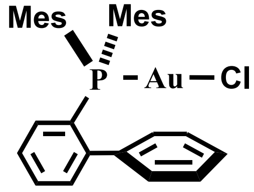


L1dAuCl (Patrick Leveque master work)

Prepared according to **the general procedure B** in 89% yield as a white powder.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.59 - 7.35 (m, 15 H), 7.29 - 7.23 (m, 1 H), 7.04 (ddd, *J* = 1.0, 7.8, 11.6 Hz, 1 H), 6.99 (dd, *J* = 1.0, 8.1 Hz, 2 H); **^{13}C NMR (101MHz, $CDCl_3$)** δ = 148.2 (d, J= 15.0 Hz, C_{quat}), 140.1 (d, J= 7.0 Hz, C_{quat}), 134.6 (d, J= 13.9 Hz, 4xCH), 133.8 (d, J= 6.6 Hz, CH), 132.1 (d, J= 8.4 Hz, CH), 131.9 (d, J= 2.2 Hz, 2xCH), 131.5 (d, J= 2.2 Hz, CH), 129.9 (d, J= 62.0 Hz, C_{quat}), 129.8 (s, 2xCH), 129.3 (d, J= 11.7, 4xCH), 128.6 (s, CH), 128.6 (s, 2xCH), 127.7 (d, J= 8.8 Hz, CH), 127.6

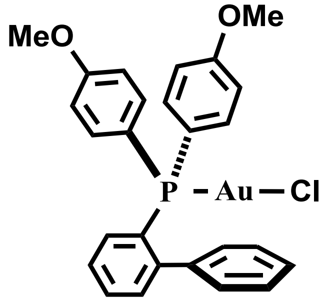
(d, J= 61.6 Hz, C_{quat}); **^{31}P NMR (121MHz, $CDCl_3$)** δ = 26.8; **HRMS (EI) m/z calcd for** $C_{24}H_{19}PAuCl$ [$(M)^+$] 570.0578, found 570.0561.



L1eAuCl (Patrick Leveque master work)

Prepared according to the **general procedure B** in 93% yield as a white powder.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.54 (tt, *J* = 1.5, 7.5 Hz, 1 H), 7.48 - 7.42 (m, *J* = 7.0 Hz, 2 H), 7.40 (dd, *J* = 7.9, 12.1 Hz, 1 H), 7.35 - 7.25 (m, 3 H), 7.16 (d, *J* = 7.5 Hz, 2 H), 6.88 (d, *J* = 3.9 Hz, 4 H), 2.31 (s, 6 H), 2.24 (s, 12 H); **^{13}C NMR (126MHz, $CDCl_3$)** δ = 148.4 (d, J= 16.5 Hz, C_{quat}), 142.5 (d, J= 10.5 Hz, 4xC_{quat}), 141.3 (d, J= 2.0 Hz, C_{quat}), 141.0 (d, J= 7.0 Hz, C_{quat}), 135.1 (d, J= 6.5 Hz, CH), 132.9 (d, J= 8.5 Hz, CH), 132.0 (d, J= 9.5 Hz, 4xCH), 131.3 (d, J= 3.0 Hz, CH), 129.5 (d, J= 56.8 Hz, C_{quat}), 129.4 (s, 2xCH), 128.8 (s, CH), 128.7 (s, 2xCH), 127.6 (d, J= 9.0 Hz, CH), 125.8 (d, J= 56.9 Hz, C_{quat}), 25.1 (d, J= 11.0 Hz, 4xCH_3), 21.1 (d, J= 1.0 Hz, 2xCH_3); **^{31}P NMR (202MHz, $CDCl_3$)** δ = 1.3; **HRMS (EI) m/z calcd for** $C_{30}H_{31}PAuCl$ [$(M)^+$] 654.1517, found 654.1511.

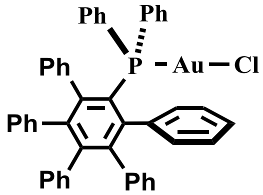


L1fAuCl

Prepared according to **general procedure B** in 81% yield as a white powder.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.54 (tt, *J* = 1.2, 7.5 Hz, 1 H), 7.45 - 7.33 (m, 7 H), 7.27 (t, *J* = 7.6 Hz, 2 H), 7.08 - 6.91 (m, 7 H), 3.85 (s, 6 H); **^{13}C NMR (101MHz, $CDCl_3$)** δ = 162.3 (d, J= 2.2 Hz, C_{quat}), 147.8 (d, J= 15.0 Hz, C_{quat}), 140.0 (d, J= 6.6 Hz, C_{quat}), 136.0 (d, J= 15.4, 4xCH), 133.4 (d, J= 7.0 Hz, CH), 131.9 (d, J= 8.1 Hz, CH), 131.1 (d, J= 2.2 Hz, CH), 129.7 (s, 2xCH), 128.7 (s, C_{quat}), 128.4 (s, CH), 128.3 (s, 2xCH), 127.4 (d, J= 9.2 Hz, CH), 120.8 (d, J= 68.2 Hz, C_{quat}), 114.7 (d, J=

13.2 Hz, 4xCH), 55.5 (s, 2xCH_3); **HRMS (EI) m/z calcd for** $C_{26}H_{23}O_2PAuCl$ [$(M)^+$] 630.0790, found 630.0791.



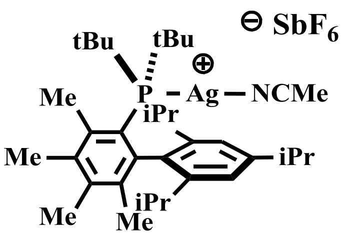
L7AuCl (Patrick Leveque master work)

Prepared according to the **general procedure B** in 89% yield as a white powder.

^{1}H NMR (500MHz, $CDCl_3$) δ = 7.49 (dd, *J* = 7.7, 13.1 Hz, 4 H), 7.17 - 6.99 (m, 6 H), 6.93 (d, *J* = 7.2 Hz, 4 H), 6.89 - 6.65 (m, 21 H); **^{13}C NMR (126MHz, $CDCl_3$)*** δ = 146.7 (d, J= 9.0 Hz, C_{quat}), 144.9 (d, J= 2.0 Hz, C_{quat}), 142.7 (d, J=7.5 Hz, C_{quat}), 139.5 (s, C_{quat}), 138.9 (d, J= 1.0 Hz, C_{quat}), 138.5 (d, J= 5.0 Hz, C_{quat}), 134.1 (d, J= 15.0 Hz, CH), 132.7 (d, J= 63.8 Hz, C_{quat}), 132.0 (s, CH), 131.0 (s, CH), 130.6 (s, CH), 130.3 (d, J= 2.5 Hz, CH), 128.3 (d, J= 12.0 Hz, CH), 127.3 (s, CH), 127.2 (d, J= 59.3 Hz, C_{quat}), 126.7 (d, J= 7.5 Hz, CH), 126.6 (s, CH), 125.9 (s, CH), 125.8 (s, CH); **^{31}P NMR (202MHz, $CDCl_3$)** δ = 37.8; **HRMS (EI) m/z calcd for** $C_{48}H_{35}AuClP$ [$(M)^+$] 874.1830, found 874.1816.

General procedure C - Synthesis of Ag(I) catalysts[1]

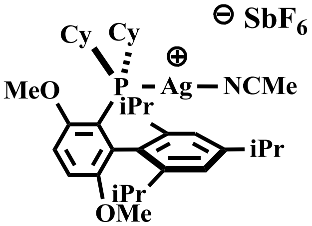
The phosphane ligand (300 mmol) dissolved in acetonitrile (5 mL) was added to a suspension of $AgSbF_6$ (300 mmol) in acetonitrile or THF (5 mL) under Ar. The reaction mixture was stirred for 2 h in the dark at RT, then the solvent was reduced to 3 mL and the solution was filtered through a Celite pad. The solvent was then evaporated to form a white solid which was triturated 2-3 times with pentane and then dried under vacuum. Crystals were obtained by slow evaporation of DCM or $CDCl_3$ at r.t.



L8aAg+ (Me$_4$tBuXPhosAgNCMeSbF$_6$) (Patrick Leveque master work)

Prepared according to the **general procedure C** in 93% yield as a white powder.

^{1}H NMR (400MHz, CDCl$_3$) δ 7.24 (s, 2 H), 2.98 (spt, *J* = 6.9 Hz, 1 H), 2.62 (s, 3 H), 2.41 (spt, *J* = 6.7 Hz, 2 H), 2.31 (s, 3 H), 2.22 (s, 3 H), 2.21 (s, 3 H), 1.46 (s, 3 H), 1.42 (s, 9 H), 1.37 (s, 9 H), 1.32 (d, *J* = 6.9 Hz, 6 H), 1.28 (d, *J* = 6.8 Hz, 6 H), 0.89 (d, *J* = 6.6 Hz, 6 H); **^{13}C NMR (101MHz, CDCl$_3$)** δ = 150.1 (s, C$_{quat}$), 146.8 (dd, J= 1.7, 1.7 Hz, 2xC$_{quat}$), 144.0 (dd, J= 27.9, 1.1 Hz, C$_{quat}$), 140.9 (d, J= 2.6 Hz, C$_{quat}$), 139.3 (d, J= 7.7 Hz, C$_{quat}$), 136.7 (d, J= 5.1 Hz, C$_{quat}$), 136.5 (d, J= 8.1 Hz, C$_{quat}$), 135.2 (dd, J= 12.1, 1.1 Hz, C$_{quat}$) , 127.2 (dd, J= 19.1, 6.2 Hz, C$_{quat}$), 123.8 (s, 2xCH), 119.3 (s, C$_{quat}$), 38.4 (dd, J= 5.9, 4.0 Hz, 2xC$_{quat}$), 34.0 (s, CH), 33.3 (dd, J= 11.9, 1.7 Hz, 6xCH$_3$), 30.8 (s, 2xCH), 27.7 (s, CH$_3$), 26.0 (s, 2xCH$_3$), 25.0 (s, 2xCH$_3$), 24.0 (s, 2xCH$_3$), 22.4 (d, J= 3.7 Hz, CH$_3$), 17.7 (s, CH$_3$), 17.4 (s, CH$_3$), 2.1 (s, CH$_3$); **^{31}P NMR (121MHz, CDCl$_3$)** δ = 63.1 (d, J(^{31}P-^{109}Ag) = 721.2 Hz), J(^{31}P-^{107}Ag) = 625.4 Hz); **HRMS (ESI) m/z calcd for** C$_{35}$H$_{56}$AgNP [(M-SbF$_6$)$^+$] 628.3201, 628.3205.

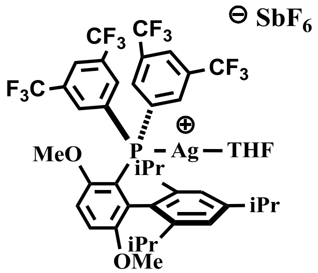


L3cAg+ (BrettPhosAgNCMeSbF$_6$) (Patrick Leveque master work)

Prepared according to the **general procedure C** in 88% yield as a white powder.

^{1}H NMR (500MHz, CDCl$_3$) δ = 7.22 (s, 2 H), 7.12 (d, *J* = 9.0 Hz, 1 H), 7.07 (d, *J* = 9.0 Hz, 1 H), 3.87 (s, 3 H), 3.75 (t, *J* = 6.4 Hz, 4 H), 3.55 (s, 3 H), 2.97 (spt, *J* = 6.8 Hz, 1 H), 2.40 (spt, *J* = 6.6 Hz, 2 H), 1.90 (quin, *J* = 3.2 Hz, 4 H), 1.32 (d, *J* = 7.2 Hz, 6 H), 1.29 (d, J= 17.0 Hz, 18 H), 1.27 (d, *J* = 6.8 Hz, 6 H), 0.90 (d, *J* = 6.6 Hz, 6 H); **^{13}C NMR (126MHz, CDCl$_3$)** δ = 155.1 (d, J= 5.0 Hz, C$_{quat}$), 152.6 (d, J= 10.5 Hz, C$_{quat}$), 150.0 (s, C$_{quat}$), 147.0 (s, 2xC$_{quat}$), 136.5 (dd, J= 21.9, 1.5 Hz, C$_{quat}$), 130.3

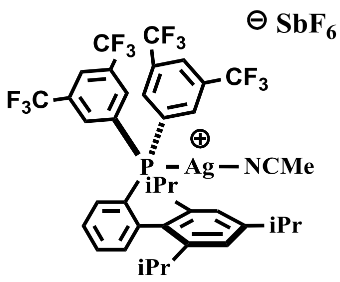
(dd, J= 11.5, 2.0 Hz, C_{quat}), 122.2 (s, 2xCH), 118.4 (dd, J= 20.9, 6.5 Hz, C_{quat}), 114.9 (d, J= 2.0 Hz, CH), 110.8 (d, J= 4.0 Hz, CH), 70.6 (s, $2xCH_2$), 54.7 (s, CH_3), 54.7 (s, CH_3), 37.1 (dd, J= 10.5, 5.0 Hz, $2xC_{quat}$), 33.8 (s, CH), 32.1 (dd, J= 11.0, 2.0 Hz, $6xCH_3$), 31.2 (s, 2xCH), 25.5 (s, $2xCH_2$), 25.2 (s, $2xCH_3$, 24.4 ($2xCH_3$), 23.7 ($2xCH_3$); **^{31}P NMR (202MHz, CDCl$_3$)** δ = 57.1 (d, J(^{31}P-^{109}Ag) = 789.8 Hz), J(^{31}P-^{107}Ag) = 683.4 Hz); **HRMS (ESI) m/z calcd for** $C_{33}H_{52}AgNO_2P$ [(M-SbF$_6$)$^+$] 632.2787, found 632.2784.



L3gAg+ (JackiePhosAgTHFSbF$_6$) (Patrick Leveque master work)

Prepared according to the **general procedure C** in 89% yield as a white powder.

^{1}H NMR (500MHz, CDCl$_3$) δ 7.94 (s, 2 H), 7.76 (d, *J* = 11.7 Hz, 4 H), 7.32 (d, *J* = 9.2 Hz, 1 H), 7.25 (s, 2 H), 7.05 (dd, *J* = 3.0, 9.1 Hz, 1 H), 3.71 - 3.68 (m, 3 H), 3.78 - 3.58 (m, 4 H), 3.38 (s, 3 H), 3.00 (spt, *J* = 6.9 Hz, 1 H), 2.39 (spt, *J* = 6.8 Hz, 2 H), 1.84 (td, *J* = 3.2, 6.7 Hz, 4 H), 1.31 (s, 6 H), 1.29 (s, 6 H), 1.03 (d, *J* = 6.8 Hz, 6 H), 0.99 (d, *J* = 6.7 Hz, 6 H); **^{13}C NMR (126MHz, CDCl$_3$)** δ = 155.1 (dd, J= 5.2, 2.7, C_{quat}), 153.1 (d, J= 12.5 Hz, C_{quat}), 151.0 (s, C_{quat}), 147.1 (s, $2xC_{quat}$), 137.0 (d, J= 26.4 Hz, C_{quat}), 132.6 (dq, J=18.5, 3.4 Hz, 4xCH), 132.4 (qd, J= 33.9, 10.5 Hz, $4xC_{quat}$), 132.1 (d, J= 36.9 Hz, $2xC_{quat}$), 129.5 (dd, J= 14.0, 1.5 Hz, C_{quat}), 124.7 (br. s., 2xCH), 122.8 (q, J= 272.8 Hz, $4xC_{quat}$), 122.5(s, C_{quat}), 117.6 (s, CH), 113.2 (dd, J= 44.9, 7.0 Hz, C_{quat}), 112.4 (d, J= 4.0 Hz, CH), 68.5 (s, $2xCH_2$), 55.5 (s, CH_3), 55.2 (s, CH_3), 34.0 (s, CH), 31.5 (s, 2xCH), 25.7 (s, $2xCH_2$), 24.6 (s, $2xCH_3$), 23.8 (s, $2xCH_3$), 23.8 (s, $2xCH_3$); **^{31}P NMR (202MHz, CDCl$_3$)** δ = -4.9 (d, J(^{31}P-^{109}Ag) = 807.3 Hz), J(^{31}P-^{107}Ag) = 700.1 Hz); **HRMS (ESI) m/z calcd for** $C_{43}H_{45}AgF_{12}O_3P$ [(M-SbF$_6$)$^+$] 975.1965, found 975.1920.



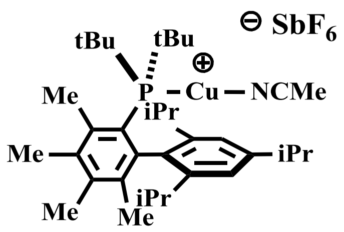
L16AgNCMeSbF$_6$ (Patrick Leveque master work)

Prepared according to the **general procedure C** in 75% yield as a white powder.

^{1}H NMR (500MHz, CDCl$_3$) δ = 8.02 (s, 2 H), 7.75 - 7.72 (m, 4 H), 7.75 (d, *J* = 11.6 Hz, 1 H), 7.63 (tt, *J* = 1.0, 7.7 Hz, 1 H), 7.41 (tt, *J* = 1.0, 7.0 Hz, 0 H), 7.35 (dt, *J* = 1.0, 8.0 Hz, 1 H), 7.24 (s, 2 H), 3.00 (spt, *J* = 7.0 Hz, 1 H), 2.24 (spt, *J* = 6.8 Hz, 2 H), 2.18 (s, 3 H), 1.32 (d, *J* = 7.0 Hz, 6 H), 1.01 (d, *J* = 7.0 Hz, 6 H), 1.00 (d, *J* = 6.7 Hz, 6 H); **^{13}C NMR (126MHz, CDCl$_3$)** δ = 151.2 (s, C$_{quat}$), 147.4 (d, J= 26.4 Hz, C$_{quat}$) , 146.7 (d, J= 1.0Hz, 2xC$_{quat}$), 134.9 (dd, J= 2.0, 20. Hz, CH), 133.3 (d, J= 1.5 Hz, CH), 133.0 (qd, J= 34.3, 10.5 Hz, 4xC$_{quat}$), 133.0 (dd, J= 16.1, 2.5 Hz, 4xCH), 133.3 (d, J= 12.0 Hz, C$_{quat}$), 132.8 (d, J= 7.5 Hz, CH), 132.5 (dd, J= 35.5, 2.8 Hz, C$_{quat}$) , 129.9 (s, CH), 129.7 (d, J= 5.5 Hz, CH), 128.0 (s, CH), 126.5 (s, CH), 125.7 (s. br., 2xCH) , 124.7 (d, J= 44.4 Hz, 2xC$_{quat}$), 122.9 (s, 2xCH), 122.6 (q, J= 274.3 Hz, 4xC$_{quat}$), 120.6 (s, CH), 119.9 (s, C$_{quat}$), 34.3 (s, CH), 31.4 (s, 2xCH), 25.2 (s, 2xCH$_3$), 23.8 (s, 2xCH$_3$), 23.3 (s, 2xCH$_3$), 2.2 (s, CH$_3$); **^{31}P NMR (202MHz, CDCl$_3$)** δ = -3.7 (d, J(^{31}P-^{109}Ag) = 785.1 Hz), J(^{31}P-^{107}Ag) = 681.6 Hz); **HRMS (ESI) m/z calcd for** $C_{39}H_{36}NF_{12}PAg$ [(M-SbF$_6$)$^+$] 884.1445, found 884.1455.

General procedure D - Synthesis of Cu(I) catalysts[1]

In a typical reaction, a flame-dried Schlenck flask (50 mL) was charged with Cu(CH$_3$CN)$_4$][X] (0.318 mmol) in DCM (2 mL) and the mixture was stirred under Ar at r.t. The desired phosphane ligand (0.318 mmol) was added, the mixture was stirred for 30 min, and then the solvent was evaporated to yield the corresponding copper(I) complex as a white solid. Crystals were obtained by slow evaporation (hexane/DCM, 10:1 v/v). (X= BF$_4$ or SbF$_6$)

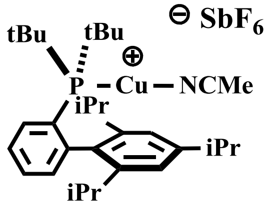


L8aCu+ (Me$_4$tBuXPhosCuNCMeSbF$_6$) (Patrick Leveque master work)

Prepared according to the **general procedure D** as a white powder.

^{1}H NMR (400MHz, CDCl$_3$) δ = 7.31 (s, 2 H), 3.00 (spt, *J* = 6.9 Hz, 1 H), 2.60 (s, 3 H), 2.40 (spt, *J* = 6.7 Hz, 2 H), 2.31 (s, 3 H), 2.28 (s, 3 H), 2.23 (s, 3 H), 1.62 (s, 1 H), 1.46 (s, 3 H), 1.38 (d, J= 15.7 Hz, 18 H), 1.33 (d, *J* = 7.0 Hz, 6 H), 1.29 (d, *J* = 6.8 Hz, 6 H), 0.90 (d, *J* = 6.6 Hz, 6 H). **^{13}C NMR (101MHz, CDCl$_3$)** δ = 151.0 (d, J= 2.2 Hz, C$_{quat}$), 145.5 (d, J= 2.2 Hz, 2xC$_{quat}$), 144.5 (d, J= 32.6 Hz, C$_{quat}$), 140.8 (d, J= 2.2 Hz, C$_{quat}$), 139.1 (s, C$_{quat}$), 136.9 (d, J= 5.5 Hz, C$_{quat}$), 136.1 (d, J= 9.5 Hz, C$_{quat}$), 130.0 (d, J= 21.6 Hz, C$_{quat}$), 129.8 (s, C$_{quat}$), 125.8 (d, J= 1.8 Hz, 2xCH), 119.3 (s, C$_{quat}$), 37.9 (d,

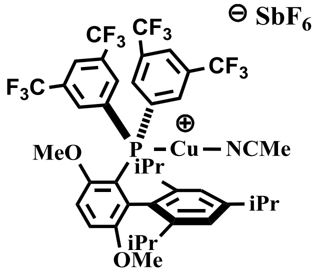
J= 9.5 Hz, 2xC$_{quat}$), 34.1 (s, CH), 32.8 (d, J= 9.5 Hz, 6xCH$_3$), 31.1 (s, 2xCH), 27.0 (s, CH$_3$), 25.6 (s, 2xCH$_3$), 25.3 (s, 2xCH$_3$), 24.2 (s, 2xCH$_3$), 22.1 (d, J= 3.3 Hz, CH$_3$), 17.6 (s, CH$_3$), 17.3 (s, CH$_3$), 2.6 (s, CH$_3$); **^{31}P NMR (121MHz, CDCl$_3$)** δ = 48.7; **HRMS (ESI) m/z calcd for** C$_{35}$H$_{56}$CuNP [(M-SbF$_6$)$^+$] 584.3446, found 584.3434



L2aCu+ (tBuXPhosCuMeCN)SbF$_6$

Prepared according to **general procedure D** as a white powder.

^{1}H NMR (400MHz, CDCl$_3$) δ = 7.84 (dt, J= 5.8 Hz, 3.5 Hz, 1H), 7.55 (dt, J = 3.1 Hz, 1.1 Hz, 2H), 7.31-7.28 (m, 3H), 3.00 (sept, J = 6.9 Hz, 1H), 2.36 (sept, J = 6.7 Hz, 2H), 1.31-1.26 (m, 30 H), 0.95 (d, J = 6.6 Hz, 6H) **^{13}C NMR (101MHz, CDCl$_3$)** δ = 150.8 (s), 146.8 (d, J = 21.9 Hz), 145. 1 (s), 134.5 (s), 133.4 (d, J = 9.1 Hz), 132.8 (d, J =7.2 Hz), 130.8 (s), 130.0 (s), 129.8 (s), 127.9 (d, J = 5.1 Hz), 124.4 (s), 118.4 (s) 35.4 (d, J =17.1 Hz), 34.1 (s), 31.2 (s), 30.9 (d, J= m8.2 Hz), 26.6 (s), 24.0 (s), 22.9 (s), 2.58 (s) **^{31}P NMR (121MHz ,CDCl$_3$)** δ = 0.00 **HRMS (ESI) m/z calcd for** $C_{32}H_{52}CuNP$ [(M-SbF$_6$)$^+$] 544.3133, found 544.5193



L3gCu+ (JackiePhosCuNCMeSbF$_6$) (Patrick Leveque master work)

Prepared according to the **general procedure D** as a white powder.

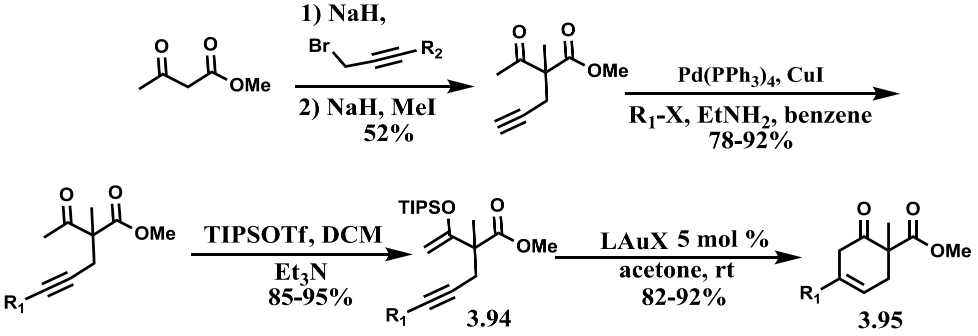
^{1}H NMR (400MHz, CDCl$_3$) δ = 7.95 (s, 2 H), 7.77 (d, *J* = 10.9 Hz, 4 H), 7.31 (d, *J* = 9.1 Hz, 1 H), 7.24 (s, 2 H), 7.08 (dd, *J* = 2.9, 9.1 Hz, 1 H), 3.69 (s, 3 H), 3.49 (s, 3 H), 3.00 (spt, *J* = 6.9 Hz, 1 H), 2.35 (spt, *J* = 6.7 Hz, 2 H), 2.13 (s, 3 H), 1.33 (s, 3 H), 1.31 (s, 3 H), 0.99 (d, *J* = 7.2 Hz, 6 H), 0.96 (d, *J* = 6.9 Hz, 6 H); **^{13}C NMR (101MHz, CDCl$_3$)** δ = 155.1 (d, J= 2.2 Hz, C$_{quat}$), 152.8 (d, J= 13.2 Hz, C$_{quat}$), 150.4 (s, C$_{quat}$), 145.4 (d, J= 1.5 Hz, 2xC$_{quat}$), 136.6 (d, J= 29.3 Hz, C$_{quat}$), 133.1 (d, J= 36.7 Hz, 2xC$_{quat}$), 133.0 (dd, J= 16.9, 2.2 Hz, 4xCH), 132.2 (qd, J= 33.7, 10.3 Hz, 4xC$_{quat}$), 128.8 (d, J= 12.5 Hz, C$_{quat}$), 124.2 (m, 2xCH), 123.4 (s, 2xCH), 122.9 (q, J= 273.3 Hz, 4xC$_{quat}$) , 118.1 (s, C$_{quat}$), 117.4 (d, J= 1.5 Hz, CH), 114.8 (d, J= 44.0 Hz, C$_{quat}$), 112.4 (d, J= 4.0 Hz, CH), 55.4 (s, CH$_3$), 55.1 (s, CH$_3$), 34.3 (s, CH), 31.6 (s, 2xCH), 24.7 (s, 2xCH$_3$), 23.8 (s, 2xCH$_3$), 22.8 (s, 2xCH$_3$), 2.0 (s, CH$_3$); **^{31}P NMR (121MHz ,CDCl$_3$)** δ = -11.5; **^{19}F NMR (377MHz, CDCl$_3$)** δ = -63.1; **HRMS (ESI) m/z calcd for** $C_{41}H_{40}CuF_{12}NO_2P$ [(M-SbF$_6$)$^+$] 900.1901, found 900.1905.

References

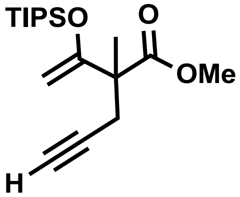
(1) Pérez-Galán, P.; Delpont, N.; Herrero-Gómez, E.; Maseras, F.; Echavarren, A. M. *Chem. Eur. J.* **2010**, 16, 5324.

Experimental Chapter 3: *Selective divergent gold(I)-catalyzed synthesis of fused carbocycles*

7.6 Detailed Experimental: *Substrate exploration, linear template*

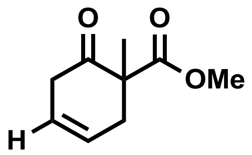


Scheme 7.05 *Synthetic sequence, linear template exploration*



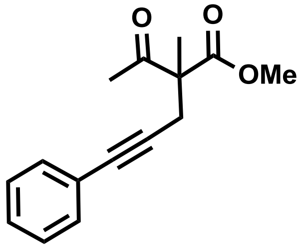
Silyl enol ether (3.94a)

β-ketoester (300 mg, 1.44 mmol), was dissolved in DCM (10 mL) and Et_3N (723 µL, 5.19 mmol) mmol) was added. The mixture was cooled to 0 °C and TBSOTf (1.1 mL, 4.3 mmol). The mixture was stirred for 8 h at 0 °C and quenched with saturated $NaHCO_3$. The aqueous layer was extracted 2 times with DCM. The organics layers was combined, dried over $MgSO_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound (**3.94a**) (415 mg, 89%) as a white solid. Spectral data is in accordance with reported data and full characterization is available through the literature[1]



Cycloalkenone (3.95a)

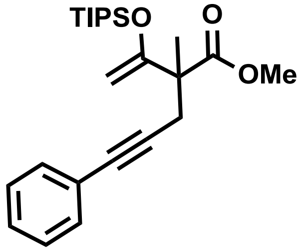
Cycloalkenone was prepared according to the **general procedure A** Gold-Catalyzed Carbocyclization and isolated as a clear oil. Spectral data is in accordance with reported data and full characterization is available through the literature[1]



β-ketoester (3.X1)

β-ketoester was prepared according to the **general procedure** F Sonogashira reaction and isolated as a clear oil.

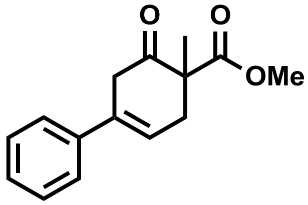
IR (neat, cm^{-1}) ν_{max} 2869, 1738, 1695, 1459, 1203; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.40-7.35 (m,2H), 7.31-7.27 (m, 3H), 3.79 (s, 3H), 2.98 (s, 1H), 2.97 (s, 1H), 2.25 (s, 3H), 1.58 (s, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 204.0 (C$_{quat}$), 192,2 (C$_{quat}$), 131.8 (CH), 128.3 (CH), 128.1 (CH), 123.3 (C$_{quat}$), 84.9 (C$_{quat}$), 83.7 (C$_{quat}$), 59.5 (C$_{quat}$), 52.9 (CH$_3$), 26.4 (CH$_3$), (C$_{quat}$), 26.1 (CH$_2$), 19.5 (CH$_3$) ; **HRMS (EI)** m/z calcd for $C_{15}H_{16}O_3$ 244.1099, found 244.1091.



Silyl enol ether (3.94b)

β-ketoester (300 mg, 1.44 mmol), was dissolved in DCM (10 mL) and Et$_3$N (723 μL, 5.19 mmol) mmol) was added. The mixture was cooled to 0 °C and TBSOTf (1.1 mL, 4.3 mmol). The mixture was stirred for 8 h at 0 °C and quenched with saturated $NaHCO_3$. The aqueous layer was extracted 2 times with DCM. The organics layers was combined, dried over $MgSO_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5)) to give the compound (**3.94b**) (415 mg, 89%) as a white solid. Spectral data is in accordance with reported data and full characterization is available through the literature[1]

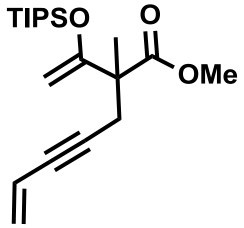
IR (neat, cm^{-1}) ν max 2957, 2869, 1733, 1652, 1276, 883; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.37-7.34 (m, 2H), 7.27-7.24 (m,3H), 4.24 (d, J = 2.5Hz, 1H), 4.22 (d, J = 2.5Hz, 1H), 3.69 (s, 3H), 3.00 (d, J = 16.7 Hz, 1H), 2.89 (d, J = 16.7 Hz, 1H), 1.50 (s, 3H), 1.27-1.18 (m, 3H), 1.08 (d, J = 7.2 Hz, 18H) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 174.6 (C_{quat}), 158.8 (C_{quat}), 131.7 (CH), 128.2 (CH), 127.7 (C_{quat}), 124.0 (CH), 88.4 (CH), 86.8 (C_{quat}), 83.0 (C_{quat}), 52.3 (C_{quat}), 52.1 (CH_3), 27.1 (CH_2), 21.0 (CH_3), 18.1 (CH), 12.9 (CH_3) ; **HRMS (EI)** m/z calcd for $C_{24}H_{36}O_3Si$ 400,2434, found 400.2436.



Cycloalkenone (3.95b)

Cycloalkenone (**3.95b**) was prepared according to the **general procedure A** Gold-Catalyzed Carbocyclization and isolated as a clear oil.

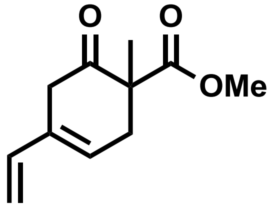
IR (neat, cm^{-1}) ν max 2946, 2856, 1735, 1712, 1653, 1188; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.36-7.33 (m, 4H), 7.31-7.26 (m, 1H), 6.25 (dddd, J =5.5 Hz, 3.4 Hz, 1.7 Hz, 1.7 Hz, 1H), 3.71 (s, 3H), 3.54 (ddd, J = 20.9 Hz, 1.7 Hz, 1.7 Hz, 1H), 3.31 (ddd, J = 21.9 Hz, 1.5 Hz, 1.5 Hz, 1H), 3.21 (dd, J = 17.7 Hz, 5.6 Hz, 1H), 2.41 (ddd, J= 17.6 Hz, 2.6 Hz, 2.6 Hz, 1H), 1.42 (s, 3H)) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 206.3 (C_{quat}),173.2 (C_{quat}), 139.1 (C_{quat}), 135.2 (C_{quat}), 128.7 (CH), 127.9 (CH), 125.2 (CH), 121.9 (CH), 55.1 (C_{quat}), 52.8 (CH_3), 41.0 (CH_2), 36.5 (CH_2), 19.8 (CH_3) ; **HRMS (EI)** m/z calcd for $C_{15}H_{16}O_3$ 244.1099 , found 244.1086.



Silyl enol ether (3.94c)

Silyl enol ether (**3.94c**) was prepared according to the **general procedure F** Sonogashira reaction and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2951, 2872, 1738, 1666, 1265, 954; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.74 (dddd, J = 17.5 Hz, 11.0 Hz,, 2.1 Hz, 2.1 Hz, 1H), 5.51 (dd, J = 17.5 Hz, 2.4 Hz, 1H), 5.36 (dd, J = 11.0 Hz, 2.3 Hz, 1H), 4.21 (d, J = 2.5 Hz, 1H), 4.18 (d, J = 2.5 Hz, 1H), 3.66 (s, 3H), 3.66 (s, 3H), 2.87 (dd, J = 16.8 Hz, 2.0 Hz, 1H), 2.80 (dd, J = 16.8 Hz, 2,1 Hz, 1H), 1.43 (s, 3H), 1.26-1.15 (m, 3H), 1.07 (d, J =7.3 Hz, 18H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 174.5 (C$_{quat}$), 158.8 (C$_{quat}$), 125.9 (CH$_2$), 117.7 (CH), 88.3 (CH$_2$), 87.5 (C$_{quat}$), 81.7 (C$_{quat}$), 52.2 (CH$_3$), 52.1 (C$_{quat}$), 27.1 (CH$_2$), 21.0 (CH$_3$), 18.1 (CH), 12.9 (CH$_3$) ; **HRMS (EI)** m/z calcd for $C_{20}H_{34}O_3Si$ 350.2277, found 350.2259.



Cycloalkenone (3.95c)

Cycloalkenone (**3.95c**) was prepared according to the **general procedure A** Gold-Catalyzed Carbocyclization and isolated as a clear oil.

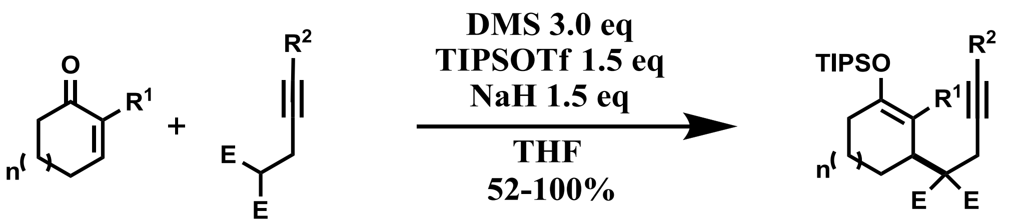
IR (neat, cm^{-1}) ν max 2946, 2856, 1735, 1712, 1653, 1188; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 6.36 (dd, J = 17.6 Hz, 10.7 Hz, 1H), 5.83 (dd, J = 4.7 Hz, 2.9 Hz, 1H), 5.04 (d, J = 6.1 Hz, 1H), 5.01 (s, 1H), 3.70 (s, 3H), 3.26 (ddd, J = 20.7 Hz, 2.0 Hz, 2.0 Hz, 1H), 3.12 (dd, J = 18.0 Hz, 5.5 Hz, 1H), 2.98 (ddd, J = 20.7 Hz, 2.0 Hz, 2.0 Hz, 1H), 2.32 (ddd, J = 18.0 Hz, 1.1 Hz, 1.1 Hz, 1H), 1.37 (s, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 206.2 (C$_{quat}$), 173.2 (C$_{quat}$), 137.4 (CH), 134.6 (C$_{quat}$), 126.2 (CH), 112.6 (CH$_2$), 55.6 (C$_{quat}$), 52.8 (CH$_3$), 38.2 (CH$_2$), 36.4 (CH$_2$), 19.9 (CH$_3$) ; **HRMS (EI)** m/z calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0937.

7.7 Detailed Experimental: *Selective divergent gold(I)-catalyzed synthesis of fused carbocycle*

General Procedure E: 1-4 addition of diethyl propargylmalonate on alkenone[2, 3]

1) To a THF suspension of NaH (2.0 mmol) was added a THF (5 mL) solution of diethyl propargylmalonate (1.5 mmol) at rt. After 20 minutes, the mixture was cooled down to 0 °C and the cycloalkenone (1 mmol) was added, followed by the addition of TIPSOTf (1.5 mmol). The mixture was stirred for 1 hour at 0 °C and quenched with a saturated solution of $NaHCO_3$. The aqueous layer was extracted three times with ethyl acetate. The organics layers were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5)) to give silyl enol ether as a clear oil. (20-65% yield).

2) To a flame-dried flask equipped with a magnetic stir bar and under argon atmosphere was added cycloalkenone (1.0 mmol) and THF (5 mL). The solution was cooled to -78 °C and TIPSOTf (1.5 mmol) was added followed by the dropwise addition of Me_2S (3.0 mmol). The reaction was stirred 30 min at -78 °C. During this time, in a separate flame-dried flask equipped with a magnetic stir bar and under argon atmosphere, a THF solution of diethyl propargylmalonate (1.5 mmol) was added to a THF (5 mL) suspension of NaH (2.0 mmol) at rt. The mixture was stirred 30 min and added dropwise to the first flask at –78°C. The reaction mixture was stirred at -78 °C for 1h and quenched with a saturated solution of $NaHCO_3$. The aqueous layer was extracted three times with ethyl acetate. The organics layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 90:10)) to give silyl enol ether as a clear oil. (52-100% yield).

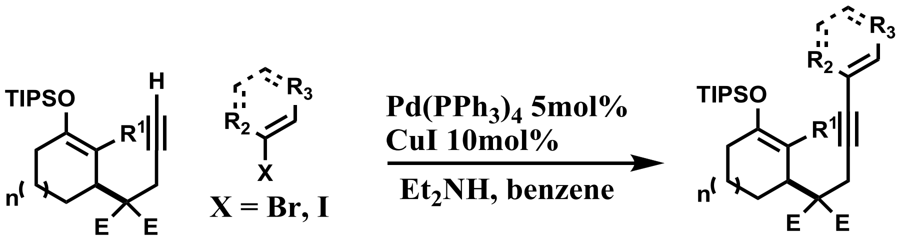


3.96

Scheme 7.06 *1-4 addition of diethyl propargylmalonate on cycloalkenon*

General Procedure F: Sonogashira reaction[4]

A flame-dried flask equipped with a magnetic stir bar was charged with $Pd(PPh_3)_4$ (0.05 mmol) followed by CuI (0.1 mmol). Benzene (10.0 mL) was then added and the solution was degassed with argon for 15 minutes. During the degassing, the terminal alkyne (1.0 mmol) was added followed by vinyl halide or aryl halide (1.5-3.0 mmol). Once the degassing was completed, diethyl amine (5.0 mmol) was added to the solution and the mixture was stirred overnight. Silica was added directly to the mixture and the solvent was evaporated off under reduced pressure. The residue was then purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5) to give the desired compound as a clear yellow oil (60-100% yield). Vinyl halides for the synthesis of compounds 8k-p were synthesized according to the literature procedures



3.96

3.96

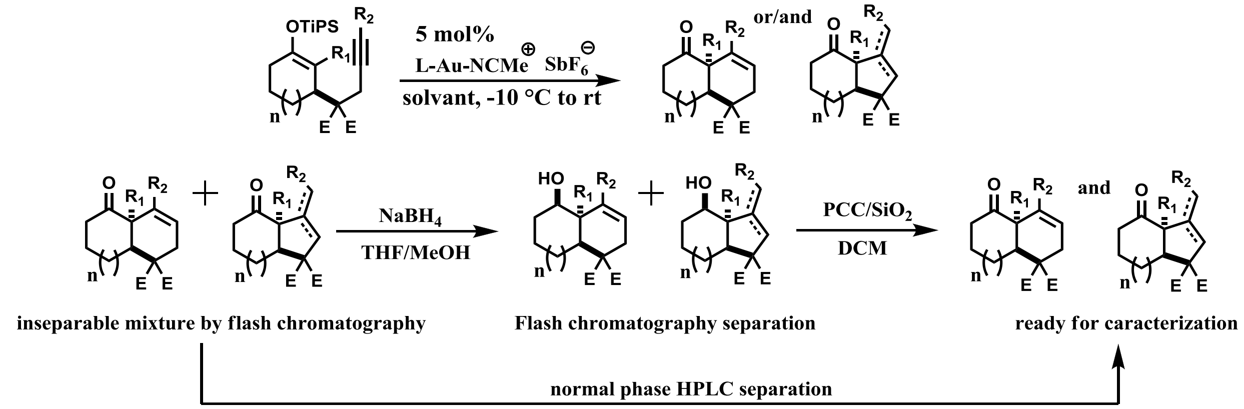
Scheme 7.07 *Sonogashira reaction*

General Procedure G: gold(I)-catalyzed carbocyclization

The flask was charged with silyl enol ether (0.175 mmol), solvent (2 mL) and the cationic gold(I) complex (0.0087 mmol, 5 mol%). The mixture was stirred for 1 to 42 hours at room temperature. The reaction was monitored by TLC. Upon completion, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel eluted with hexane/AcOEt (9:1 to 6:1) to give the cyclization products.

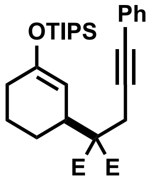
Note 1: The flasks were always kept in a base bath prior to performing the reaction. (Base Bath preparation: KOH pellets (70 g) were dissolved in *i*PrOH (1L) and distilled water (200 mL)). The flasks from the base bath were washed with water, rinsed with acetone prior usage and dry in the oven (60 °C) for 10-20 minutes.

Note 2: When DCM was used as the solvent, dry conditions were necessary for reproducibility of these results. The round bottom flask was flame-dried and the solvent distilled over CaH_2.



Scheme 7.08 *Gold(I)-catalyzed carbocyclization, separation and purification*

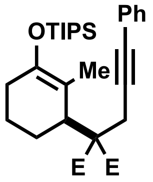
Detailed experimental for substrates with terminal alkynes or internal alkynes (R2 =Me) is presented in Experimental Chapter 5.



Silyl enol ether (3.96b)

Silyl enol ether **(3.96b)** was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as colorless oil.

IR (neat, cm^{-1}) ν max 2944, 2867, 1730, 1653, 1188, 883; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40-7.32 (m, 2H), 7.28-7.25 (m, 3H), 4.94-4.92 (m, 1H), 4.21 (dddd, J = 10.9 Hz, 7.2 Hz, 7.2 Hz, 7.2 Hz, 2H), 4.21 (dddd, J = 10.9 Hz, 7.2 Hz, 7.2 Hz, 7.2 Hz, 2H), 3.29-3.22 (m, 1H), 3.04 (s, 2H), 2.15-1.98 (m, 2H), 1.97-1.82 (m, 2H), 1.66-1.58 (m, 1H), 1.49-1.39 (m, 1H), 1.27 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.27 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.17-1.10 (m, 3H), 1.07 (d, J =7.3 Hz, 18H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.2 (C_{quat}), 170.0 (C_{quat}), 131.9 (CHx2), 128.3 (CHx2), 127.9 (CH), 123.7 (C_{quat}), 104.0 (CH), 85.9 (C), 83.1 (C_{quat}), 61.5 (C_{quat}), 61.4 (CH_2), 60.9 (CH_2), 39.1 (CH), 29.8 (CH_2), 24.4 (CH_2), 23.2 (CH_2), 22.7 (CH_2), 18.1 (C_{quat}), 17.9 (CH_3x6), 14.2 (CH_3), 14.2 (CH_3), 12.7 (CHx3); **HRMS (EI)** m/z calcd for $C_{31}H_{46}O_5Si$ [M^+] 526. 3115, found 326. 3118.

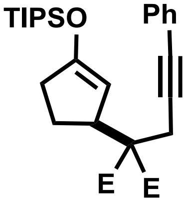


Silyl enol ether (3.96d)

Silyl enol ether **(3.96d)** was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as colorless oil.

IR (neat, cm^{-1}) ν max 2944, 2867, 1730, 1653, 1188, 883; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.37-7.33 (m, 2H), 7.28-7.23 (m, 3H), 4.21 (dt, J = 13.1 Hz, 7.2 Hz, 4H), 3.39-3.34 (br, 1H), 3.07 (d, J = 16.9 Hz, 1H), 3.01 (d, J = 16.9 Hz, 1H), 2.12-2.01 (m, 2H), 1.80-1.74 (m, 2H), 1.67 (s, 3H), 1.60-1.53 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.25 (t, J =7.2 Hz, 3H), 1.15-1.10 (m, 3H), 1.07 (d, J =7.3 Hz, 18H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.8 (C_{quat}), 170.7 (C_{quat}), 131.7 (CHx2), 128.3 (CHx2), 127.7 (CH), 124.0 (C_{quat}), 110.8 (C_{quat}), 87.0 (C_{quat}), 82.7 (C_{quat}), 61.5 (C_{quat}), 61.5 (CH_2), 61.4 (CH_2), 43.2 (CH), 30.3 (CH_2), 25.8 (CH_2), 24.7 (CH_2), 21.4 (CH_2), 18.4 (CH_3x6), 18.3 (C), 15.5 (CH_3), 14.2

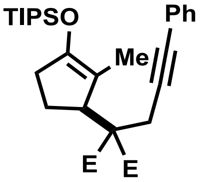
(CH_3), 14.1 (CH_3), 13.4 (CHx3); **HRMS (EI)** m/z calcd for [M^+] $C_{32}H_{48}O_5Si$ 540.3271, found 540.3284.



Silyl enol ether (3.96f)

Silyl enol ether (**3.96f**) was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as a colorless oil.

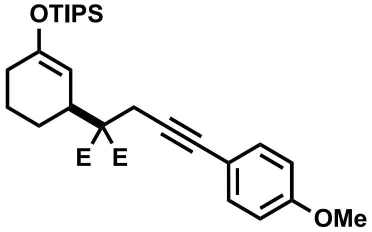
IR (neat, cm^{-1}) ν max 2944-2867, 1733, 1645, 1252; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38-7.33 (m, 2H), 7.29-7.26 (m,3H), 4.75 (ddd, J = 1.9 Hz, 1.6 Hz, 1.6 Hz, 1H), 4.36,-4.13 (m, 4H), 3.69-3.64 (m,1H), 3.04 (d, J = 17.1 Hz, 1H), 2.98 (d, J = 17.1 Hz, 1H), 2.32-2.27 (m, 2H), 2.15-2.05 (m, 1H), 1.97-1.88 (m, 1H), 1.28 (t, J = 7.1 Hz,, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.21-1.13 (m, 3H), 1.06 (d, J =7.0 Hz, 18H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 170.4 (C$_{quat}$), 170.2 (C$_{quat}$), 157.2 (C$_{quat}$), 131.7 (CHx2), 128.3 (CHx2), 127.9 (CH), 123.7 (C$_{quat}$), 102.7 (CH), 85.8 (C$_{quat}$), 82.9 (C$_{quat}$), 61.4 (CH$_2$x2), 61.0 (C$_{quat}$), 45.8 (CH), 33.1 (CH$_2$), 23.8 (CH$_2$), 23.3 (CH$_2$), 18.0 (CH$_3$x6), 14.2 (CH$_3$x2), 12.5 (CHx3); **HRMS (EI)** m/z calcd for $C_{30}H_{44}O_5Si$ [M$^+$] 512.2958, found 512.2958.



Silyl enol ether (3.96h)

Silyl enol (**3.96h**) ether was prepared according to the general **procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as colorless oil.

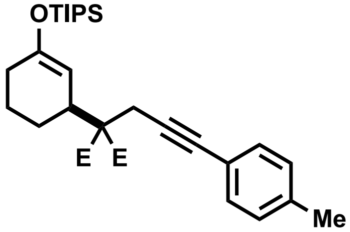
IR (neat, cm^{-1}) ν max 3057, 2980-2874, 1734, 1492, 1297, 1027; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.38-7.34 (m,2H), 7.29-7.26 (m, 3H), 4.26-4.16 (m, 4H), 3.66-3.61 (m, 1H), 3.15 (d J =17.3 Hz, 1H), 2.99 (d, J = 17.3 Hz, 1H), 2.47-2.38 (m, 1H), 2.26-2.13 (m, 2H), 2.09-2.01 (m, 1H), 1.59 (s, 3H), 1.29 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.27 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.16-1.11 (m, 3H), 1.10-1.06 (m, 18H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 170.5 (C$_{quat}$), 170.2 (C$_{quat}$), 150.9 (C$_{quat}$), 131.6 (CHx2), 128.2 (CHx2), 127.8 (CH), 123.8 (C$_{quat}$), 111.8 (C$_{quat}$), 86.4 (C$_{quat}$), 82,6 (C$_{quat}$), 61.5 (CH$_2$), 61.4 (CH$_2$), 61.2 (C$_{quat}$), 49.1 (CH), 32.4 (CH$_2$), 23.8 (CH$_2$), 23.3 (CH$_2$), 18.0 (CH$_3$x6), 14.2 (CH$_3$), 14.1 (CH$_3$), 13.0 (CHx3), 11.9 (CH$_3$); **HRMS (EI)** m/z calcd for [M$^+$] $C_{31}H_{46}O_5Si$ 526.3115, found 526.3105.



Silyl enol ether (3.96j)

Silyl enol ether (**3.96j**) was prepared according to the **general procedure F** Sonogashira reaction from silyl enol ether (**3.96b**) and isolated as a colorless oil.

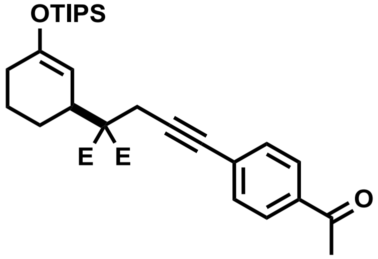
IR (neat, cm^{-1}) ν max 2943, 2867, 1730, 1511, 1248, 1195, 1035; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.29-7.26 (m, 2H), 6.81-6.77 (m, 2H), 4.94-2.92 (m, 1H), 4.21 (dt, J = 11.1 Hz,, 7.2 Hz,, 4H), 3.79 (s, 3H), 3.28-3.22 (m, 1H), 3.02 (s, 2H), 2.12-1.80 (m, 4H), 1.67-1.55 (m, 1H), 1.48-1.38 (m, 1H), 1.26 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.26 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.19-1.10 (m, 3H), 1.06 (d, J =7.2 Hz, 18H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 170.3 (C$_{quat}$), 170.1 (C$_{quat}$), 159.3 (C$_{quat}$), 152.8 (C$_{quat}$), 133.1 (CHx2), 116.0 (C$_{quat}$), 113.9 (CHx2), 104.1 (CH), 84.2 (C$_{quat}$), 82.9 (C$_{quat}$), 61.4 (CH$_2$), 61.4 (CH$_2$), 61.0 (C$_{quat}$), 55.4 (CH$_3$), 39.0 (CH), 29.8 (CH$_2$), 24.4 (CH$_2$), 23.4 (CH$_2$), 22.7 (CH$_2$), 18.1 (CH$_3$x6), 14.2 (CH$_3$), 14.1 (CH$_3$), 12.7 (CHx3); **HRMS (EI)** m/z calcd for [M$^+$] $C_{32}H_{48}O_6Si_1$ 556.3220, found 556.3237.



Silyl enol ether (3.96k)

Silyl enol ether (**3.96k**) was prepared according to the **general procedure F** Sonogashira reaction from silyl enol ether (**3.96b**) and isolated as a colorless oil.

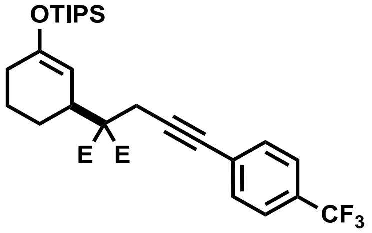
IR (neat, cm^{-1}) ν max 3028, 2942, 2865, 1733, 1662, 1511, 1196 1036; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.23 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 7.9 Hz, 2H), 4.93 (s, 1H), 4.20 (m, J = 11.1 Hz, 7.2 Hz, 4H), 3.28-3.22 (m, 1H), 3.02 (s, 2H), 2.32 (s, 3H), 2.16-2.05 (m, 1H), 2.01-1.80 (m, 3H), 1.66-1.54 (m, 1H), 1.48-1.39 (m, 1H), 1.26 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.24 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.19-.109 (m, 3H), 1.06 (d, J = 6.0 Hz, 18H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 170.2 (C$_{quat}$), 170.0 (C$_{quat}$), 152.7 (C$_{quat}$), 137.8 (C$_{quat}$), 131.5 (CHx2), 129.0 (CHx2), 120.6 (C$_{quat}$), 104.0 (CH), 84.9 (C$_{quat}$), 83.1 (C$_{quat}$), 61.4 (CH$_2$), 61.3 (CH$_2$), 60.9 (C$_{quat}$), 39.0 (CH), 29.8 (CH$_2$), 24.3 (CH$_2$), 23.2 (CH$_2$), 22.6 (CH$_2$), 21.5 (CH$_3$), 18.1 (CH$_3$x6), 14.2 (CH$_3$), 14.2 (CH$_3$), 12.6 (CHx3); **HRMS (EI)** m/z calcd for $C_{32}H_{48}O_5Si$ [(M-$C_5H_{10}O_2$)$^+$] 497.2723, found



Silyl enol ether (3.96l)

Silyl enol ether (**3.96l**) was prepared according to the **general procedure F** Sonogashira reaction from silyl enol ether (**3.96b**) and isolated as a yellow oil.

IR (neat, cm^{-1}) ν max 2943, 2867, 1735, 1685, 1367, 1263, 1195, 1073; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.84 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 4.89 (s, 1H), 4.27-4.13 (m, 4H), 3.26-3.20 (m, 1H), 3.03 (s, 2H), 2.56 (s, 3H), 2.15-2.04 (m, 1H), 2.01-1.92 (m, 1H), 1.90-1.81 (m, 2H), 1.65-1.53 (m, 1H), 1.45-1.36 (m, 1H), 1.25 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.24 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.16-1.08 (m, 3H), 1.03 (d, J = 6.5 Hz, 18H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 197.4 (C$_{quat}$), 170.0 (C$_{quat}$), 169.8 (C$_{quat}$), 153.0 (C$_{quat}$), 136.0 (C$_{quat}$), 131.8 (CHx2), 128.6 (C$_{quat}$), 128.2 (CHx2), 103.7 (CH), 89.9 (C$_{quat}$), 82.5 (C$_{quat}$), 61.5 (CH$_2$), 61.4 (CH$_2$), 60.8 (C$_{quat}$), 39.1 (CH), 29.7 (CH$_2$), 26.7 (CH$_3$), 24.4 (CH$_2$), 23.2 (CH$_2$), 22.5 (CH$_2$), 18.0 (CH$_3$x6), 14.2 (CH$_3$), 14.1 (CH$_3$) 12.6 (CHx3); **HRMS (EI)** m/z calcd for $C_{33}H_{48}O_6Si$ [M$^+$] 568.3220, found 568.3247.

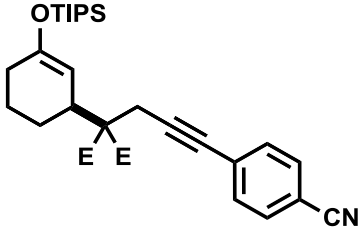


Silyl enol ether (3.96m)

Silyl enol ether (**3.96m**) was prepared according to the **general procedure F** Sonogashira reaction from silyl enol ether (**3.96b**) and isolated as a yellow-orange oil.

IR (neat, cm^{-1}) ν max 2944, 2868, 1734, 1663, 1465, 1324, 1168, 1068; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.51 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 4.90 (s, 1H), 4.30-4.15 (m, 4H), 3.27-3.20 (m, 1H), 3.04 (s, 2H), 2.16-2.05 (m, 1H), 2.01-1.94 (m, 1H), 1.91-1.82 (m, 2H), 1.64-1.54 (m, 1H), 1.46-1.35 (m, 1H), 1.26 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.25 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.17-1.08 (m, 3H), 1.05 (d, J =6.4 Hz, 18H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 170.0 (C$_{quat}$), 169.9 (C$_{quat}$), 153.0

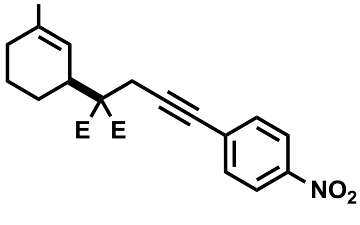
(C_{quat}), 131.9 (CHx2), 130.2 (CH), 125.4 (C_{quat}), 125.2 (q, $J_{C\text{-}F}$ = 3.9 Hz) (CHx2), 124.9 (q, $J_{C\text{-}F}$ = 3.9 Hz) (C_{quat}), 103.8 (CH), 88.9 (C_{quat}), 81.9 (C_{quat}), 61.5 (CH_2), 61.5 (CH_2), 60.9 (C_{quat}), 39.2 (CH), 29.8 (CH_2), 24.4 (CH_2), 23.1 (CH_2), 22.6 (CH_2), 18.1 (CH_3x6), 14.2 (CH_3), 14.2 (CH_3) 12.7 (CHx3); **HRMS (EI)** m/z calcd for $C_{32}H_{45}F_3O_5Si_1$ [M^+] 594.2988, found 594.3012.



Silyl eno ether (3.96n)

Silyl enol ether (**3.96n**) was prepared according to the **general procedure F** Sonogashira reaction from silyl enol ether (**3.96b**) and isolated as a yellow oil.

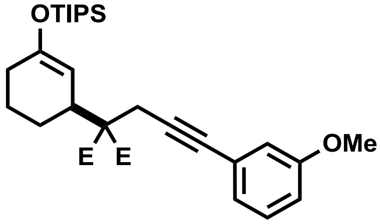
IR (neat, cm^{-1}) ν max 2966, 2862, 1733, 1672, 1367, 1195, 1073; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 (d, J = 8.6 Hz, 2H), 7.40 (d, 8.6 Hz, 2H), 4.88 (s, 1H), 4.26-4.15 (m, 4H), 3.21 (d, J = 9.2 Hz, 1H), 3.03 (s, 2H), 2.14-2.04 (m, 1H), 2.00-1.92 (m, 1H), 1.85 (dd, J = 10.4 Hz, 4.0 Hz, 2H), 1.63-1.52 (m, 1H), 1.44-1.33 (m, 1H), 1.25 (t, J = 7.1 Hz, 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 7.1 Hz, 3H), 1.17-1.07 (m, 3H), 1.02 (d, J =7.2 Hz, 18H) **; ^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.9 (C_{quat}), 169.7 (C_{quat}), 153.1 (C_{quat}), 132.2 (CHx2), 131.9 (CHx2), 128.6 (C_{quat}), 118.6 (C_{quat}), 111.2 (C_{quat}), 103.6 (CH), 91.3 (C_{quat}), 81.7 (C_{quat}), 61.6 (CH_2), 61.5 (CH_2), 60.8 (C_{quat}), 39.2 (CH), 29.8 (CH_2), 24.4 (CH_2), 23.1 (CH_2), 22.6 (CH_2), 18.1 (CH_3x6), 14.3 (CH_3), 14.2 (CH_3) 12.7 (CHx3); **HRMS (EI)** m/z calcd for $C_{32}H_{45}NO_5Si_1$ 551.3027, found 571.3054



Silyl enol ether (3.96o)

Silyl enol ether (**3.96o**) was prepared according to the **general procedure F** Sonogashira reaction Sonogashira reaction from silyl enol ether (**3.96b**) and isolated as a yellow oil.

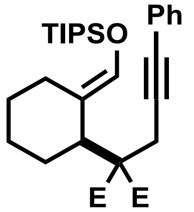
IR (neat, cm^{-1}) ν max 2943, 2866, 1733, 1662, 1594, 1520, 1464m 1343, 1195; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.11 (dd, J = 8.9 Hz, 2.2 Hz, 2H), 7.45 (dd, 8.9 Hz, 2.2 Hz, 2H), 4.98-4.87 (m, 1H), 4.24-4.15 (m, 4H), 3.25-3.19 (m, 1H), 3.04 (s, 2H), 2.15-2.04 (m, 1H), 2.00-1.92 (m, 1H), 1.88-1.81 (m, 2H), 1.63-1.52 (m, 1H), 1.43-1.33 (m, 1H), 1.24 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.24 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.14-1.07 (m, 3H), 1,03 (d, J =7.3 Hz, 18H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 169.9 (C$_{quat}$), 169.7 (C$_{quat}$), 153.1 (C$_{quat}$), 146.9 (C$_{quat}$), 132.4 (CHx2), 130.6 (C$_{quat}$), 123.5 (CHx2), 103.6 (CH), 92.4 (C$_{quat}$), 81.6 (C$_{quat}$), 61.6 (CH$_2$), 61.5 (CH$_2$), 60.8 (C$_{quat}$), 39.3 (CH), 29.8 (CH$_2$), 24.4 (CH$_2$), 23.2 (CH$_2$), 22.6 (CH$_2$), 18.0 (CH$_3$x6), 14.2 (CH$_3$), 14.2 (CH$_3$) 12.7 (CHx3); **HRMS (EI)** m/z calcd for [M$^+$] $C_{31}H_{45}NO_7Si$ 571.2965, found 571.2980.



Silyl enol ether (3.96p)

Silyl enol ether was prepared according to the **general procedure F** Sonogashira reaction and isolated as a clear oil.

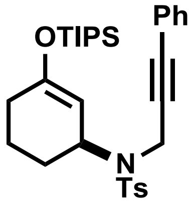
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.18 (ddd, J = 8.8 Hz, 7.7 Hz, 1.1 Hz, 1H), 6.94 (ddd, J = 7.7 Hz, 1.1 Hz, 1H), 6.88-6.86 (m, 1H), 6.82 (ddd, J = 8.3 Hz, 2.7 Hz, 0.9 Hz, 1H), 4.92-4.90 (m, 1H), 4.21 (dt, J = 11.0 Hz, 7.1 Hz, 2H), 3.78 (s, 3H), 3.27-3.23 (m, 1H), 3.02 (s, 2H), 2.14-2.06 (m, 1H), 2.00-1.81 (m, 3H), 1.62-1.56 (m, 2H), 1.25 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.25 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.25 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.14-1.09 (m, 3H), 1.06 (d, J =7.2 Hz, 18H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 170.2 (C$_{quat}$), 170.0(C$_{quat}$), 159.3 (C$_{quat}$), 152.8 (C$_{quat}$), 129.3 (CH), 124.7 (C$_{quat}$), 124.3 (CH), 116.6 (CH), 114.3 (CH), 103.9 (C$_{quat}$), 85.8 (C$_{quat}$), 83.0 (C$_{quat}$), 61.5 (CH$_2$) 61.4 (CH$_2$), 60.9 (C$_{quat}$),55.4 (CH$_3$), 39.0 (CH), 29.8 (CH$_2$), 24.4 (CH$_2$), 23.2 (CH$_2$), 22.6 (CH$_2$), 18.1 (CH$_3$), 18.1 (CH$_3$), 14.2 (CH$_3$), 14.2 (CH$_3$), 12.6 (CH); **HRMS (EI)** m/z calcd for $C_{32}H_{48}O_6Si_1$ 556.3220, found 556.3210



Silyl enol ether (3.96q)

Silyl enol ether was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone in 58% yield as a clear oil.

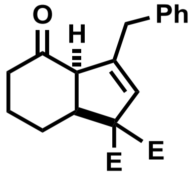
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34-7.31 (m, 2H), 7.27-7.23 (m, 3H), 6.48 (s, 1H), 4.31-4.09 (m, 4H), 3.13-3.10 (m, 1H), 3.08 (d, J = 16.9 Hz, 1H), 3.01 (d, J = 16.9 Hz, 1H), 2.57 (dt, J = 13.4 Hz, 3.7 Hz, 1H), 2.19-2.12 (m, 1H), 1.86-1.75 (m, 2H), 1.61-1.49 (m, 2H), 1.39-1.30 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.13-1.06 (m, 3H), 1.03 (d, J =7.1 Hz, 18H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.9 (C$_{quat}$), 170.7 (C$_{quat}$), 136.4 (CH), 131,6 (CH), 128.2 (CH), 127.8 (CH), 123.7 (C$_{quat}$), 118.2 (C$_{quat}$), 86.2 (C$_{quat}$), 83.4 (C$_{quat}$), 61.6 (CH$_2$), 61.4 (CH$_2$), 59.8 (C$_{quat}$), 41.4 (CH), 29.4 (CH$_2$), 26.6 (CH$_2$), 26.0 (CH$_2$), 23.7 (CH$_2$), 22.9 (CH$_2$), 17.9 (CH$_3$), 14.2 (CH$_3$), 14.0 (CH$_3$), 12.1 (CH)**; HRMS (EI) m**/z calcd for $C_{32}H_{48}O_5Si$ 540.3271, found 540.3255.



Silyl enol ether (3.96r)

Silyl enol ether was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone in 58% yield as a clear oil.

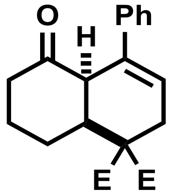
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.88-7.80 (m, 2H), 7.30-7.19 (m, 7H), 4.71-4.66 (m,,1H), 4.43 (t J= 2.1 Hz, 1H), 4,27 (t, J = 18.1 Hz, 1H), 2.35 (s, 3H), 2,14-2.05 (m, 1H), 1.84-1.79 (m,1H), 1.62-1.49 (m, 1H), 1.20 (d, J= 9.8 Hz, 2H), 1.04-0.95 (m, 21H) ;**^{13}C NMR (100 MHz, CDCl$_3$)** δ 156.2 (C$_{quat}$), 143.1 (C$_{quat}$), 132.6 (C$_{quat}$), 131.6 (CH), 129.5 (CH), 128.2 (CH), 127.5 (CH), 123.0 (C$_{quat}$), 102.9 (CH), 86.2 (C$_{quat}$), 83.8 (C$_{quat}$), 55.5 (CH), 33.4 (CH$_2$), 29.5 (CH$_2$), 28.2 (CH$_2$), 21.6 (CH$_3$), 21.1 (CH$_2$), 18.0 (CH$_3$),17.8 (CH), 12.4 (CH) ; **HRMS (EI)** m/z calcd for $C_{31}H_{43}NO_5SSi$ [M$^+$] 537. 2733, found 537.2762



Bicyclo[3.4.0]alkenone (3.98b)

Bicyclo[3,4,0]alkenone (**3.98b**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2987, 2932, 1736, 1454, 1254, 1238, 1153; **mp (°C)** 116.9-118.7 ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.27-7.22 (m, 2H), 7.20-7.16 (m, 1H), 7.13-7.10 (m, 2H), 6.60 (d, J = 1.8Hz, 1H), 4.29-4.12 (m, 4H), 3.80 (d, J= 7.5 Hz, 1H), 3.54 (ddd, J = 17.4 Hz, 2.3 Hz, 2.3 Hz, 1H), 3.34 (ddd, J = 12.3 Hz, 6.1 Hz, 6.1 Hz, 1H), 3.02 (d, J = 17.4 Hz, 1H), 2.21-2.13 (m, 1H), 2.07-2.02 (m,1H), 1.95-1.87(m, 1H), 1.74-1.61 (m, 2H), 1.43 (ddd, J = 12.6, 12.6 Hz, 3.8Hz, 1H), 1.26 (t, J = 7.2 Hz, 6H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 210.2 (C$_{quat}$), 171.1 (C$_{quat}$), 169.5 (C$_{quat}$), 137.9 (C$_{quat}$), 136.2 (C$_{quat}$), 128.9 (CHx2), 128.1 (CHx2), 127.2 (CH), 126.8 (CH), 62.0 (C), 61.9 (CH$_2$), 56.9 (CH), 49.2 (CH), 40.5 (CH$_2$), 39.0 (CH$_2$), 24.9 (CH$_2$), 24.1 (CH$_2$), 14.2 (CH$_3$), 14.1 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{22}H_{26}O_5$ [M$^+$] 370.1780, found 370.1792.

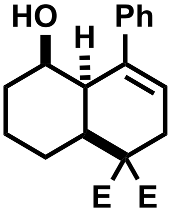


Bicyclo[4.4.0]alkenone (3.99b)

Bicyclo[4,3,0]alkenone (**3.99b**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **JohnPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2980, 2941, 2867, 1732, 1444, 1254, 1180, 1044; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.26-7.16 (m, 5H), 5.94 (ddd, J = 5.4 Hz, 2.7 Hz, 2.7 Hz, 1H), 4.27-4.15 (m, 4H), 3.94 (br, 1H), 3.08-3.00 (m, 1H), 3.04-3.00 (m, 1H), 2.82 (ddd, J = 19.3 Hz, 4.3 Hz, 2.5 Hz, 1H), 2.10-1.96 (m, 3H), 1.71-1.59 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 211.7 (C$_{quat}$), 170.0 (C$_{quat}$), 169.7 (C$_{quat}$), 140.0 (C$_{quat}$), 134.4 (C$_{quat}$), 128.3 (CHx2), 127.5 (CH), 127.2 (CHx2), 124.6 (CH), 62.0 (CH$_2$), 61.9 (CH$_2$), 56.2 (C$_{quat}$), 53.0 (CH), 40.9 (CH), 39.9 (CH$_2$), 27.5

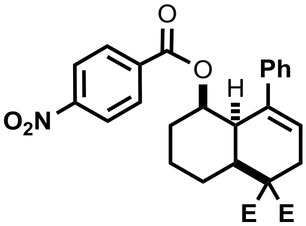
(CH_2), 26.1 (CH_2), 23.6 (CH_2), 14.1 (CH_3), 14.1 (CH_3); **HRMS (EI)** m/z calcd for $C_{22}H_{26}O_5$ [M^+] 370.1780, found 370.1778.



Bicyclo[4,4,0]alkenol (3.X2)

Bicycloakenol was prepared according to a general procedure for the reduction of ketone with $NaBH_4$ in MeOH/THF and isolated as a clear oil.

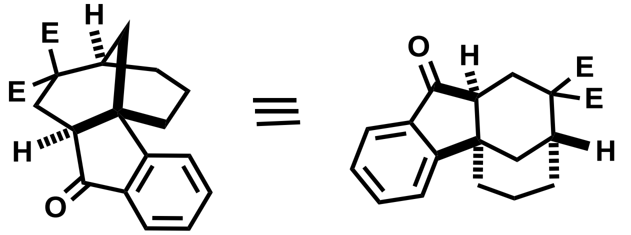
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (m, 5H), 5.64-5.61 (m, 1H), 4.25-4.17 (m, 4H), 3.74-3.66 (m, 1H), 345 (br, 1H), 2.91 (ddd, J = 4.5 Hz, 3.0 Hz, 2.8 Hz, 1H), 2.86 (ddd, J= 4.5 Hz, 2.8 Hz, 0.9 Hz,, 1H), 2.70-2.62 (m, 2H), 1.80-1.76 (m, 1H), 1.65-1.60 (m, 1H), 1.44-1.47 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), , 1.26 (t, J = 7.1 Hz, 3H) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.6 (C_{quat}), 170.4 (C_{quat}), 143.2 (C_{quat}), 138.5 (C_{quat}), 128.5 (CHx2), 128.0 (CHx2), 127.3 (CH), 127.1 (CH), 74.2 (CH), 61.8 (CH_2), 61.6 (CH_2), 57.6 (C_{quat}), 42.5 (CH), 38.9 (CH), 31.1 (CH_2), 23.2 (CH_2), 23.0 (CH_2), 14.2 (CH_3); **HRMS (EI)** m/z calcd for $C_{22}H_{28}O_5$ 372.1937, found 372.1963.



Bicyclo[4,4,0]alkenoate (3.X3)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.9 Hz, 2.1 Hz, 2H), 7.40 (dd, 8.9 Hz, 2.1 Hz, 2H), 7.09-7.02 (m, 5H), 5.60-5.56 (m, 1H), 5.15 (ddd, J = 9.8 Hz, 4.8 Hz, 4.8 Hz, 1H), 4.23 (dq, J = 14.2 Hz, 7.2 Hz, 2H), 4.23 (dq, J = 14.2 Hz, 7.2 Hz, 2H), 3.76 (br, 1H), 2.93-2.82 (m, 1H), 2.88-2.85 (m 1H), 2.75 (ddd, J = 4.0 Hz, 2.2 Hz, 2.2 Hz, 1H), 1.90-1.83 (m, 1H), 1.77-1.69 (m, 2H), 1.63-1.45 (m, 3H), 1.28 (dd, J= 7.1 Hz, 7.1 Hz, 3H), 1.28 (dd, J= 7.1 Hz, 7.1 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.4(C_{quat}), 170.2 (C_{quat}), 163.8 (C_{quat}), 150.4 (C_{quat}), 144.5 (C_{quat}), 138.3 (C_{quat}), 135,7 (C_{quat}), 130.8 (CHx2), 128.2 (CH), 127.5 (CHx2), 127.3 (CHx2), 126.2 (CH), 123.0 (CHx2), 76.8 (CH), 61.9

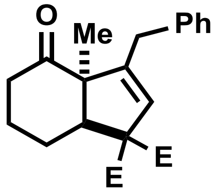
(CH_2x2), 57.4 (C_{quat}), 40.0 (CH), 38.5 (CH), 27.7 (CH_2), 27.3 (CH_2), 23.2 (CH_2), 23.0 (CH_2), 14.2 (CH_3); **HRMS (EI)** m/z calcd for $C_{20}H_{31}O_8$ [$(M-C_{22}H_{27}O_4)^+$] 355.1909, found 355.1917.



Benzofuran (3.111)

The flask was charged with silyl enol ether (**3.96b**) (0.175 mmol), DCM (2 mL) and triflic acid (5eq). The mixture was stirred for 1 hour at room temperature. The reaction was monitored by TLC. Upon completion, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel eluted with hexane/AcOEt (9:1 to 6:1) to give the benzofuran products in 88% yield.

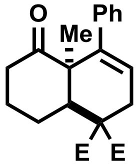
IR (neat, cm^{-1}) ν max 2974, 2938, 2877, 1742, 1711, 1452, 1234, 1052; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.73 (dt, J = 7.6 Hz, 1.0 Hz, 1H), 7.59 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.36 (td, J = 7.4 Hz, 1.0 Hz, 1H), 4.32-4.09 (m, 4H), 2.95-2.90 (m, 1H), 2.87 (t J = 6.4 Hz, 1H), 2.73 (t, J = 6.8 Hz, 1H), 2.30 (dd, J =15.0 Hz, 6.6 Hz, 1H), 2.05-1.95 (m, 1H), 1.80-1.57 (m, 7H), 1.27 (t, J= 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 206.12 (C$_{quat}$), 172.1 (C$_{quat}$), 171.4 (C$_{quat}$), 161.9 (C$_{quat}$), 134.9 (CH), 134.6 (C$_{quat}$), 127.7 (CH), 124.2 (CH), 123.3 (CH), 61.7 (CH$_2$), 61.4 (CH$_2$), 55.9 (C$_{quat}$), 51.3 (CH), 41.3 (C$_{quat}$), 37.8 (CH$_2$), 36.3 (CH$_2$), 33.5 (CH), 27.3 (CH$_2$), 20.7 (CH$_2$), 14.2 (CH$_3$), 14.1 (CH$_3$); **HRMS (EI)** m/z calcd for [M$^+$] $C_{22}H_{26}O_5$ = 370.1780



Bicyclo[3.4.0]alkenone (3.98d)

Bicyclo[3,4,0]alkenone (**3.98d**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2982, 2940, 2867, 1732, 1711, 1445, 1256, 1178, 1049; **mp (°C)** 79.7 - 82.3; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.24-7.12 (m, 4H), 7.04 (dd, J = 7.3 Hz, 0.9 Hz, 1H), 6.55 (s, 1H), 4,28-4.10 (m, 4H), 3.63 (dd, J = 18.0 Hz, 1.9 Hz, 1H), 3.31 (dd, J = 17.9 Hz, 1.4 Hz, 1H), 3.12 (dd, J = 11.4 Hz, 5.1 Hz, 1H), 2.08-2.02 (m, 1H), 1.94-1.81 (m, 2H), 1.57-1.44 (m, 3H), 1.31-1.24 (m, 6H), 1.27 (s, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 211.8 (C$_{quat}$), 171.8 (C$_{quat}$), 169.7 (C$_{quat}$), 144.5 (C$_{quat}$), 136.4 (C$_{quat}$), 129.0 (CHx2), 127.9 (CHx2), 127.2 (CH), 124.9 (CH), 62.5 (C), 62.1 (CH$_2$), 60.3(C), 57.1 (CH), 40.3 (CH$_2$), 39.2 (CH$_2$), 25.8 (CH$_2$), 25.4 (CH$_2$), 23.1 (CH$_3$), 14.2 (CH$_3$), 14.1 (CH$_3$); **HRMS (EI)** m/z calcd for [M$^+$] $C_{23}H_{28}O_5$ 384.1937, found 384.1927.

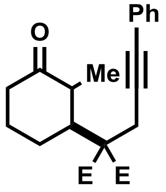


Bicyclo[4.4.0]alkenone (3.99d)

Bicyclo[4,4,0]alkenone (**3.99d**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **Me$_4$tBuXPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 3062, 2981, 2941 1731, 1297, 1232, 1096; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.24-7.12 (5H), 5.92 (dd, J = 4.8 Hz, 2.2 Hz, 1H), 4.30-4.10 (m,4H), 3.29 (dd, J = 19.6 Hz, 4.9 Hz, 2H), 2,94 (dd, J = 11.7 Hz, 7.9 Hz, 1H), 2.76 (dd, J = 19.6 Hz, 3.2 Hz, 1H), 2.28-2.15 (m, 1H), 2.01-1.81 (m, 2H), 1.75-1.62 (m, 2H), 1.42 (s, 3H), 1.31-1.24 (m, 6H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ

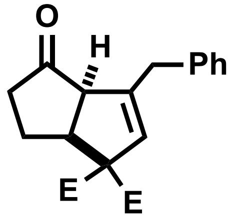
212.1 (C_{quat}), 170.9 (C_{quat}), 170.4 (C_{quat}), 140.6 (C_{quat}), 139.6 (C_{quat}), 128.3 (CHx2), 127.8 (CH), 127.3 (CHx2), 125.6 (CH), 62.0 (CH_2), 62.0 (CH_2), 56.4 (C_{quat}), 55.4 (C_{quat}), 49.1 (CH), 40.9 (CH_2), 27.5 (CH_2), 26.2 (CH_2), 25.9 (CH_2), 23.0 (CH_3), 14.1 (CH_3), 13.9 (CH_3); **HRMS (EI)** m/z calcd for [M^+] $C_{23}H_{28}O_5$ 384.1937, found 384.1932.

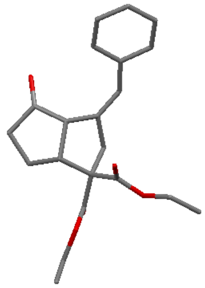


Ketone (3.105d)

Ketone (**3.105d**) was prepared as a secondary product according to the **general procedure G** Gold-Catalyzed Carbocyclization and isolated as a clear oil..

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.27-7.23 (m, 3H), 4.27-4.17 (m, 4H), 3.07 (s, 2H), 2.82-2.76 (m, 2H), 2.44 (ddd, J = 14.3 Hz, 12.8 Hz, 6.6 Hz, 1H), 2.25 (dd, J = 12.8 Hz, 1H), 2.11-2.01 (m, 2H), 1.94-1.82 (m, 1H), 1.70-1.57(m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.08 (d, J = 7.2 Hz, 3H) **; ^{13}C NMR (100 MHz, $CDCl_3$)** δ 213.5 (C_{quat}), 170.4 (C_{quat}), 169.9 (C_{quat}), 131.8 (CHx2), 128.3 (CHx2), 128.1 (CH), 123.2 (C_{quat}), 84.2 (C_{quat}), 84.0 (C_{quat}), 61.9 (CH2), 61.8 (CH2), 59.5 (C_{quat}), 46.8 (CH), 43.3 (CH), 37.5 (CH_2), 25.4 (CH_2), 24.3 (CH_2), 22.9 (CH_2), 14.2 (CH_3x2), 12.2 (CH_3); **HRMS (EI)** m/z calcd for $C_{23}H_{28}O_5$ 384.1937, found 384.1917.

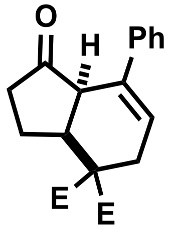




Bicyclo[3,3,0]alkenone (3.98f)

Bicyclo[3,3,0]alkenone (**3.98f**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

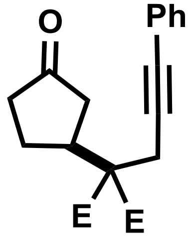
IR (neat, cm^{-1}) ν max 2980-2891, 1703, 1368, 1259, 1067; **mp (°C)** 85.3-88.7; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.62-7.57 (m, 2H), 7.34-7.22(m, 3H), 6.54-6.52 (m, 1H), 4.26 (dddd, J = 10.7 Hz, 7.2 Hz, 7.2 Hz, 7.2 Hz, 2H), 4.18 (q, J =7.1 Hz, 2H), 3.78-3.67 (m, 2H), 3.16 (ddd, J =15.6 Hz, 1.9 Hz, 1,9 Hz, 1H), 2.82 (d, J = 15.9 Hz, 1H), 2.51-2.33 (m, 2H), 2.16-2.07 (m, 1H), 1.64-1.54 (m, 1H), 1.29 (t, J = 7,2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 215.8 (C$_{quat}$), 170.9 (C$_{quat}$), 169.6 (C$_{quat}$), 136.4 (C$_{quat}$), 135.7 (C$_{quat}$), 128.4 (CH), 128.0 (CHx2), 128.0 (CH), 127.5 (CHx2), 62.2 (C$_{quat}$), 61.9 (CH$_2$), 61.8 (CH$_2$), 53.2 (CH), 45.6 (CH), 42.3 (CH$_2$), 39.7 (CH$_2$), 23.0 (CH$_2$), 14.3 (CH$_3$), 14.2(CH$_3$); **HRMS (EI)** m/z calcd for $C_{21}H_{24}O_5$ [M$^+$] 356.1623, found 356.1609.



Bicyclo[4,3,0]alkenone (3.99f)

Bicyclo[4,3,0]alkenone (**3.99f**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **Me$_4$tBuXPhos**AuNCMeSbF$_6$ as catalyst or **general procedure H2** with **t-BuXPhos**AgNCMeSbF$_6$ and isolated as a clear oil.

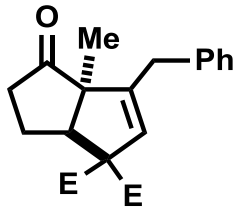
IR (neat, cm^{-1}) ν max 2994-2855, 1729, 1236, 1097; **mp (°C)** 69.6- 72.5; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.32-7.19 (m, 5H), 5.86 (ddd, J =4.4 Hz, 4.4 Hz, 2.2 Hz, 1H), 4.30-4.07 (m, 4H), 3.88 (dd, J = 7.8 Hz, 1.5 Hz, 1H), 3.34 (ddd, J = 12.0 Hz, 7.5 Hz, 7.5 Hz, 1H), 2.86 (dd, J = 4.2 Hz, 2.9 Hz, 2H), 2.33-2.12 (m, 2H), 1.92-1.84 (m, 1H), 1.75 (ddd, J = 12.2 Hz, 9.2 Hz, 2.8 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 214.0 (C$_{quat}$), 170.7 (C$_{quat}$), 170.3 (C$_{quat}$), 140.1 (C$_{quat}$), 134.3 (C$_{quat}$), 128.1 (CHx2), 127.4 (CH), 126.9 (CHx2), 123.4 (CH), 61.9 (CH$_2$), 61.8 (CH$_2$), 55.1 (C$_{quat}$), 50.0 (CH), 39.7 (CH), 36.8 (CH$_2$), 26.7 (CH$_2$), 22.6 (CH$_2$), 14.3 (CH$_3$), 14.1 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{21}H_{24}O_5$ [M$^+$] 356.1623, found 356.1635.



Ketone (3.105f)

Ketone (**3.10g**) was prepared as a secondary product according to the **general procedure G** gold-catalyzed carbocyclization and isolated as a clear oil.

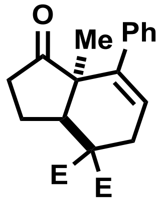
IR (neat, cm^{-1}) ν max 3004-2869, 1738, 1695, 1459, 1203 ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.35-7.32 (m, 2H), 7.30-7.24 (m, 3H), 4.30-4.17 (m, 4H), 3.18-3.04 (m, 2H), 3.09 (d, J = 8.9 Hz, 1H), 2.62 (dd, J = 18.8 Hz, 17.5 Hz, 1H), 2.38-2.16 (m, 4H), 1.83-1.72 (m, 1H), 1.27 (t, J = 7.2 Hz, 6H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 217.6 (C$_{quat}$), 169.6 (C$_{quat}$), 169.5 (C$_{quat}$), 1314 (CHx2), 128.3 (CH), 123.0 (C$_{quat}$), 84.2 (C$_{quat}$), 83.9 (C), 61.9 (CH$_2$), 61.8 (CH$_2$), 59.4 (C$_{quat}$), 41.4 (CH$_2$), 39.8 (CH), 38.7 (CH$_2$), 25.1 (CH$_2$), 24.6 (CH$_2$), 14.2 (CH$_3$x2); **HRMS (EI)** m/z calcd for [M$^+$] $C_{21}H_{24}O_5$ 356.1634, found 356.1611.



Bicyclo[3.3.0]alkenone (3.98h)

Bicyclo[3,3,0]alkenone (**3.98h**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

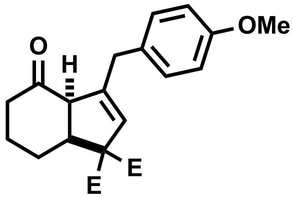
IR (neat, cm^{-1}) ν max 2983, 1734, 1469, 1257, 1153; **mp (°C)** 68.6-70.4; **^{1}H NMR (400 MHz, CDCl$_3$)** δ ppm 7.43 (dd, J = 6.9 Hz, 0.6 Hz, 1H) 7.33-7.12 (m, 4 H) , 6.62 (s, 1H), 4.32-4.15 (m, 4H), 3.35 (dd, J=16.4, 2.4 Hz, 1H), 3.28 (dd, J = 7.9 Hz, 7.9 Hz, 1H), 3.02 (ddd, J=16.5 Hz, 1.3 Hz, 1.3 Hz, 1H), 2.32 (dd, J=16.6 Hz, 2.3 Hz, 1H), 2.32 (s, 1H), 2.04 (dddd, J=13.7 Hz, 8.4 Hz, 8.4 Hz, 6.7 Hz, 1H), 1.67-1.49 (m, 1H) 1.28 (ddd, J = 7.1Hz, 7.1 Hz, 4.0 Hz, 6H), 1.16 (s, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 216.6 (C), 171.1 (C), 169.7 (C), 140.7 (C), 136.3 (C), 129.3(CHx2), 127.7 (CHx2), 127.6 (CH), 127.1 (CH), 62.0 (C), 61.9 (CH$_2$), 61.8(CH$_2$), 59.5 (C), 54.7 (CH), 43.3 (CH$_2$), 37.1 (CH$_2$), 21.9 (CH$_2$), 21.8 (CH$_3$), 14.3(CH$_3$), 14.2 (CH$_3$); **HRMS (EI)** m/z calcd for [M$^+$] $C_{22}H_{27}O_5$ 371.1859, found 371.1887.



Bicyclo[4.3.0]alkenone (3.99h)

Bicyclo[4,3,0]alkenone (**3.99h**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **Me_4tBuXPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2976, 2941, 2904, 1734, 1492, 1444, 1257; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.24-7.21 (m, 3H), 6.94-6.91 (m, 2H), 5.67 (dd, J = 5.7 Hz, 2.5 Hz, 1H), 4.32-4.21 (m, 2H), 4.21-4.12 (m, 2H), 3.11 (dd, J = 18.4 Hz, 6.1 Hz, 1H), 3.05 (dd, J = 11.1 Hz, 7.0 Hz, 1H), 2.57 (dd, J = 18.7 Hz, 2.3 Hz, 1H), 2,50 (dt, J = 9.5 Hz, 2.3 Hz, 1H), 2.41-2.34 (m, 1H), 2.30-2.20 (m, 1H), 1.87-1.76 (m, 1H), 1.29 (t, J = 7.1 Hz, 6H), 1.13 (s, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 216.1 (C), 170.3 (C), 170.2 (C), 140.5 (C), 137.9 (C), 129.4 (CHx2), 127.5 (CH), 127.2 (CHx2), 126.3 (CH), 61.9 (CH$_2$x2), 54.3 (C), 54.3 (C), 46.8 (CH), 35.2 (CH$_2$), 27.2 (CH$_2$), 22.0 (CH$_2$), 21.7 (CH$_3$), 14.2 (CH$_3$), 14.1 (CH$_3$); **HRMS (EI)** m/z calcd for [M$^+$] $C_{22}H_{26}O_5$ 370.1780, found 370. 1777.

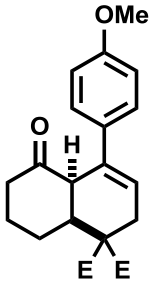


Bicyclo[3.4.0]alkenone (3.98j)

Bicyclo[3,4,0]alkenone (**3.98j**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2980, 2920, 1730, 1701, 1511, 1250, 1176; **^{1}H NMR (300 MHz, CDCl$_3$)** δ 7.04 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.9 Hz, 2H), 6.51 (d, J = 2.1 Hz, 1H), 4.30-4.20 (m, 4H), 3.81-3.15 (m, 1H), 3.76 (s, 3H), 3.52 (ddd, J = 17.6 Hz, 2.4 Hz, 2.4 Hz, 1H), 3.52 (ddd, J = 12.4 Hz, 6.5 Hz, 5.6 Hz, 1H), 3.02 (d, J = 17.6 Hz, 1H), 2.23-2.13 (m, 1H), 2.07-1.99 (m, 1H), 1.96-1.85 (m, 1H), 1.74-1.56 (m, 2H), 1.42 (qd, J = 13.2 Hz, 3.9 Hz, 1H), 1.25 (t, J = 7.1 Hz, 6H), 1.25 (t, J = 7.1 Hz, 6H); **^{13}C NMR (75 MHz, CDCl$_3$)** δ 210.6 (C$_{quat}$), 171.1 (C$_{quat}$), 169.5 (C$_{quat}$), 158.7 (C$_{quat}$), 136.2 (C$_{quat}$), 130.1 (CHx2), 128.8 (C$_{quat}$), 126.3 (CHx2), 113.4 (CH), 62.0 (C$_{quat}$), 61.9 (CH$_2$), 61.8 (CH$_2$), 57.0 (CH), 55.2

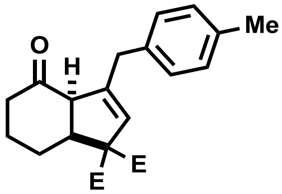
(CH$_3$), 49.2 (CH), 40.3 (CH$_2$), 39.9 (CH$_2$), 24.9 (CH$_2$), 24.2 (CH$_2$), 14.2 (CH$_3$), 14.1 (CH$_3$); **HRMS (EI)** m/z calcd for [M$^+$] $C_{23}H_{28}O_6$ 400.1886, found 400.1855.



Bicyclo[4.4.0]alkenone (3.99j)

Bicyclo[4,3,0]alkenone (**3.99j**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **JohnPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

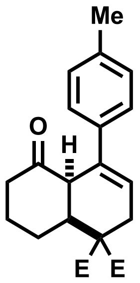
IR (neat, cm^{-1}) ν max 2982, 2940, 1733, 1714, 1609, 1512, 1245, 1181; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.16-7.13 (m, 2H), 6.80-6.76 (m, 2H), 5.87 (ddd, J = 5.4 Hz, 2.6 Hz, 2.6 Hz, 1H), 4.21 (dq, J = 16.4 Hz, 7.1 Hz, 2H), 4.21 (dq, J = 16.4 Hz, 7.1 Hz, 2H), 3.91 (br, 1H), 3.76 (s, 3H), 3.06-2.98 (m, 1H), 3.03-2.98 (m, 1H), 2.81 (ddd, J = 4.6 Hz, 2.5 Hz, 2.5 Hz, 1H), 2.10-1.97 (m, 3H), 1.71-1.59 (m, 3H), 1.26 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.24 (dd, J = 7.1 Hz, 7.1 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 212.0 (C$_{quat}$), 170.1 (C$_{quat}$), 169.8 (C$_{quat}$), 133.8 (C$_{quat}$), 132.6 (C$_{quat}$), 128.4 (CHx2), 123.3 (CHx2), 113.6 (CH), 62.0 (CH$_2$), 61.9 (CH$_2$), 56.2 (C$_{quat}$), 55.3 (CH), 53.0 (CH$_3$), 40.9 (CH), 39.9 (CH$_2$), 27.5 (CH$_2$), 26.1 (CH$_2$), 23.6 (CH$_2$), 14.2 (CH$_3$), 14.1 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{23}H_{28}O_6$ [M$^+$] 400.1886, found 400.1874.



Bicyclo[3.4.0]alkenone (3.98k)

Bicyclo[3,4,0]alkenone (**3.98k**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

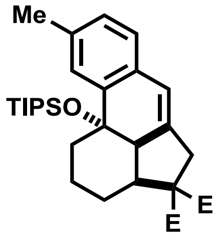
IR (neat, cm^{-1}) ν max 2975-2865, 1738, 1714, 1260, 1235, 1182; **mp (°C)** 69.0 –75.3; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.08-6.98 (m, 4H), 6.55 (d, J = 1.5 Hz, 1H), 4.28-4.11 (m, 4H), 3.79 (d, J = 7.4 Hz, 1H), 3.52 (ddd, J = 17.4 Hz, 2.3 Hz, 2.3 Hz, 1H), 3.32 (ddd, J = 12.3 Hz, 6.2 Hz, 6.2 Hz, 1H), 3.01 (d, J = 17.4 Hz, 1H), 2.28 (s, 3H), 2.21-2.13 (m, 1H), 2.07-1.97 (m, 1H), 1.94-1.86 (m, 1H), 1.71-1.57 (m, 2H), 1.47-1.37 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H) , 1.23 (t, J = 7.1 Hz, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 210.4 (C$_{quat}$), 171.1 (C$_{quat}$), 169.5 (C$_{quat}$), 137.0 (C$_{quat}$), 136.9 (C$_{quat}$), 133.3 (C$_{quat}$), 128.7 (CHx2), 128.7 (CH), 126.6 (CHx2), 61.9 (C), 61.9 (CH$_2$x2), 56.9 (CH), 49.2 (CH), 40.4 (CH$_2$), 38.9 (CH$_2$), 24.9 (CH$_2$), 24.1 (CH$_2$), 21.3 (CH$_3$) 14.2 (CH$_3$), 14.1 (CH$_3$);



Bicyclo[4.4.0]alkenone (3.99k)

Bicyclo[4,3,0]alkenone (**3.99k**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **JohnPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

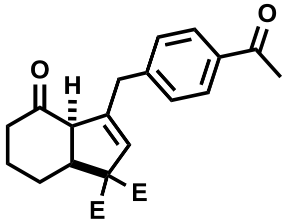
IR (neat, cm^{-1}) ν max 2979, 2941, 2866, 1733, 1714, 1445, 1234, 1180,1044; **mp (°C)** 89.5-91.6 ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.12-7.03 (m, 4H), 5.91 (ddd, J = 5.4 Hz, 2.6 Hz, 2.6 Hz, 1H), 4.27-4.15 (m, 4H), 3.91 (br, 1H), 3.07-2.99 (m, 2H), 2.81 (ddd, J = 19.2 Hz, 2.5 Hz, 1.7 Hz, 1H), 2.27 (s, 3H), 2.07-1.98 (m, 3H), 1.70-1.62 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 211.9 (C$_{quat}$), 170.0 (C$_{quat}$), 169.7 (C$_{quat}$), 137.2 (C$_{quat}$), 137.1 (C$_{quat}$), 134.3 (C$_{quat}$), 129.0 (CHx2), 127.0 (CHx2), 123.9 (CH), 62.0 (CH$_2$), 61.9 (CH$_2$), 56.2 (C$_{quat}$), 53.0 (CH), 40.9 (CH), 39.9 (CH$_2$), 27.5 (CH$_2$), 26.1 (CH$_2$), 23.6 (CH$_2$), 21.2 (CH$_3$), 14.2 (CH$_3$), 14.1 (CH$_3$); **HRMS (EI)** m/z calcd for C$_{23}$H$_{28}$O$_5$ [M$^+$] 384.1937, found 384.1928



Tricyclo[3,2,3]undecadiene (3.X4)

Tricyclo[3,2,3]undecadiene was prepared according to the **general procedure G** Gold-Catalyzed Carbocyclization a with **IPr**AuNCMeSbF$_6$ as catalyst nd isolated as a clear oil.

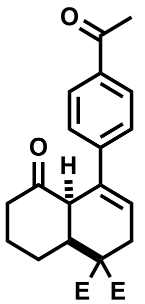
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32 (d, J = 1.1 Hz, 1H), 6.94 (dd, J = 7.5 Hz, 1.1 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.22 (d, J = 2.6 Hz, 1H), 4.31-4.09 (m, 4H), 3.44 (ddd, J = 19.2 Hz, 2.9 Hz, 2.9 Hz, 1H), 3.24 (br, 1H), 3.11-3.07 (m, 1H), 3.03 (d, J = 19.3 Hz, 1H), 2.30 (s, 3H), 1.80 (qdd, J = 13.2 Hz, 2.6 Hz, 2.6 Hz, 1H), 1.54-1.44 (m, 3H), 1.40-1.32 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.05 (dd, J = 7.4 Hz, 2.3 Hz, 18H), 0.99-0.87 (m, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.5 (C$_{quat}$), 170.0 (C$_{quat}$), 142.7 (C$_{quat}$), 140.7 (C$_{quat}$), 136.2 (C$_{quat}$), 130.3 (C$_{quat}$), 127.8 (CH), 126.0 (CH), 125.7 (CH), 119.9 (CH), 77.8 (C$_{quat}$), 63.0 (C$_{quat}$), 61.6 (CH$_2$x2), 49.8 (CH), 41.9 (CH), 39.2 (CH$_2$), 35.5 (CH$_2$), 24.2 (CH$_2$), 21.5 (CH$_3$), 19.7 (CH$_2$), 19.0 (CHx3), 18.8 (CH$_3$x6), 14.3 (CH$_3$), 14.2 (CH$_3$) **HRMS (EI)** m/z calcd for $C_{32}H_{48}O_5Si$ [$(M-C_5H_{10}O_2)^+$] 497.2723, found 497, 2738



Bicyclo[3,4,0]alkenone (3.98l)

Bicyclo[3,4,0]alkenone (**3.98l**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

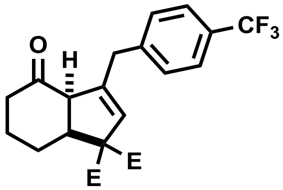
IR (neat, cm^{-1}) ν max 2973, 2947, 1730, 1698, 1256, 1233, 1043; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.84 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 6.61 (d, J = 1.8 Hz, 1H), 4.29-4.12 (m, 4H), 3.84 (d, J = 7.6 Hz, 1H), 3.55 (ddd, J = 17.6 Hz, 2.4 Hz, 2.4 Hz, 1H), 3.37 (ddd, J = 11.6 Hz, 7.2 Hz, 5.6 Hz, 1H), 3.03 (d, J = 17.6 Hz, 1H), 2.56 (s, 3H), 2.20-2.04 (m, 2H), 1.96-1.87 (m, 1H), 1.76-1.62 (m, 2H), 1.48-1.38 (m, 1H), 1.26 (t, J = 7.1 Hz, 6H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 209.5 (C$_{quat}$), 197.7 (C$_{quat}$), 171.0 (C$_{quat}$), 169.3 (C$_{quat}$), 141.0 (C$_{quat}$), 140.1 (C$_{quat}$), 135.6 (C$_{quat}$), 128.9 (CHx2), 128.2 (CHx2), 126.0 (CH), 62.0 (CH$_2$), 61.9 (CH$_2$), 61.8 (C$_{quat}$), 56.8 (CH), 49.0 (CH), 40.9 (CH$_2$), 39.0 (CH$_2$), 26.7 (CH$_3$), 24.6 (CH$_2$), 24.1 (CH$_2$), 14.2 (CH$_3$), 14.1 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{24}H_2O_6$ [M^+] 412.1886, found 412.1879.



Bicyclo[4,4,0]alkenone (3.99l)

Bicyclo[4,4,0]alkenone (**3.99l**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **Me$_4$tBuXPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2977-2869, 1733, 1684, 1268, 1168, 1057; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.84 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.06 (ddd, J = 5.4 Hz, 2.7 Hz, 2.7 Hz, 1H), 4.28-4.16 (m, 4H), 3.96 (br, 1H), 3.10-3.02 (m, 2H), 2.85 (ddd, J = 19.5 Hz, 4.2 Hz, 2.6 Hz, 1H), 2.55 (s, 3H), 2.03-1.98 (m, 3H), 1.70-1.62 (m, 3H), 1.26 (dd, J = 7.1 Hz, 7.1 Hz 3H), 1.26 (dd, J = 7.1 Hz, 7.1 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 211.2 (C$_{quat}$), 197.7 (C$_{quat}$), 169.8 (C$_{quat}$), 169.6 (C$_{quat}$), 144.6 (C$_{quat}$), 136.0 (C$_{quat}$), 133.7 (C$_{quat}$), 128.5 (CHx2), 127.4 (CHx2), 126.6 (CH), 62.1 (CH$_2$), 62.0 (CH$_2$), 56.1 (C$_{quat}$), 52.8 (CH), 40.8 (CH), 39.8 (CH$_2$), 27.6 (CH$_2$), 26.7 (CH$_3$), 25.9 (CH$_2$), 23.6 (CH$_2$), 14.2 (CH$_3$), 14.1 (CH$_3$); **HRMS (EI)** m/z calcd for [M$^+$] C$_{24}$H$_{28}$O$_6$ 412.1886, found 412.1881.

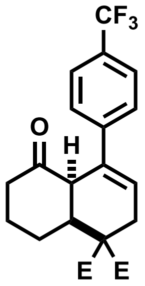


Bicyclo[3.4.0]alkenone (3.98m)

Bicyclo[3,4,0]alkenone (**3.98m**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2983-2877, 1732, 1616, 1263, 1122, 1067; **mp (°C)** 73.8-76.6; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.48 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H), 6.60 (s, 1H), 4.29-4.11 (m, 4H), 3.81 (d, J = 7.7 Hz, 1H), 3.53 (ddd, J = 17.5 Hz, 2.2 Hz, 2.2 Hz, 1H), 3.38 (ddd, J = 11.5 Hz, 7.4 Hz, 5.8 Hz, 1H), 3.01 (d, J = 17.5 Hz, 1H), 2.20-2.06 (m, 2H), 1.95-1.87 (m, 1H), 1.71-1.62 (m, 2H), 1.48-1.37 (m, 1H), 1.26 (t, J = 6.9 Hz, 3H), 1.26 (t, J = 6.9 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 209.6 (C$_{quat}$), 171.0 (C$_{quat}$), 169.5 (C$_{quat}$), 140.1 (C$_{quat}$), 139.8 (C$_{quat}$), 139.8 (C$_{quat}$), 129.0 (CHx2), 127.5 (q,

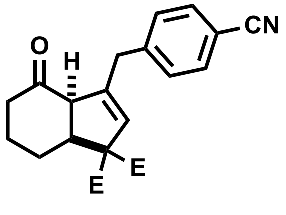
J_{C-F} = 266.0 Hz) (C), 125.7 (CH), 125.1 (q, J_{C-F} = 3.8 Hz) (CHx2), 62.0 (CH_2), 62.0 (CH_2), 61.8 (C), 56.7 (CH), 48.9 (CH), 40.9 (CH_2), 39.0 (CH_2), 24.4 (CH_2), 24.1 (CH_2), 14.2 (CH_3), 14.2 (CH_3); **HRMS (EI)** m/z calcd for $C_{23}H_{25}F_3O_5$ [M^+] 438.1654, found 438.1684.



Bicyclo[4.4.0]alkenone (3.99m)

Bicyclo[4,4,0]alkenone (**3.99m**) was prepared according to the general procedure G gold-catalyzed carbocyclization with **Me$_4$tBuXPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

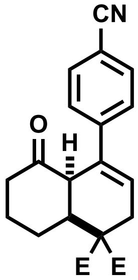
IR (neat, cm^{-1}) ν max 2981-2875, 1734, 1326, 1236, 1122, 1069; **mp (°C)** 59.5-61.9; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.50 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.33, 6.03 (ddd, J = 5.4 Hz, 2.6 Hz, 2.6 Hz, 1H), 4.29-4.10 (m, 4H), 3.96 (br, 1H), 3.10-3.03 (m, 2H), 2.85 (ddd, J = 19.5 Hz, 4.2 Hz, 2.5 Hz, 1H), 2.06-1.96 (m, 3H), 1.71-1.62 (m, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 211.1 (C_{quat}), 169.8 (C_{quat}), 169.4 (C_{quat}), 143.5 (C_{quat}), 133.6 (C_{quat}), 129.6 (C_{quat}), 129.0 (CHx2), 127.4 (q, J_{C-F} = 271.8) (C_{quat}), 126.7 (CH), 125.3 (q, J_{C-F} = 3.7 Hz) (CHx2), 62.1 (CH_2), 62.0 (CH_2), 61.9 (C_{quat}), 52.7 (CH), 40.8 (CH), 39.0 (CH_2), 27.6 (CH_2), 25.8 (CH_2), 23.7 (CH_2), 14.2 (CH_3), 14.1 (CH_3); **HRMS (EI)** m/z calcd for $C_{23}H_{25}O_5F_3$ [M^+] 438.1654, found 438.1688.



Bicyclo[3,4,0]alkenone (3,98n)

Bicyclo[4,3,0]alkenone (**3.98n**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

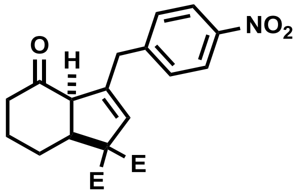
IR (neat, cm^{-1}) ν max 2987-2871**,** 2227, 1733, 1723, 1240, 1040 ; **mp (°C)** 118.1-121.3 **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.51 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 6.57 (d, J = 1.6 Hz, 1H), 4.28-4.11 (m, 4H), 3.80 (d, J = 7.7 Hz, 1H), 3.52 (ddd, J = 17.6 Hz, 2.4 Hz, 2.4 Hz, 1H), 3.37 (ddd, J = 11.4 Hz, 7.4 Hz, 5.9 Hz, 1H), 3.00 (d, J = 17.7 Hz, 1H), 2.15-2.09 (m, 2H), 1.95-1.87 (m, 1H), 1.74-1.63 (m, 2H), 1.46-1.35 (m, 1H), 1.25 (t, J = 6.9 Hz, 3H), 1.25 (t, J = 6.9 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 209.1 (C$_{quat}$), 170.9 (C$_{quat}$), 169.3 (C$_{quat}$), 141.3 (C$_{quat}$), 140.8 (C$_{quat}$), 131.9 (CHx2), 129.3 (CHx2), 125.4 (CH), 119.0 (C$_{quat}$), 62.0 (CH$_2$), 61.9 (CH$_2$), 61.7 (C$_{quat}$), 56.5 (CH), 48.7 (CH), 41.0 (CH$_2$), 39.0 (CH$_2$), 24.3 (CH$_2$), 24.0 (CH$_2$), 14.1 (CH$_3$), 14.1 (CH$_3$) ;**HRMS (EI)** m/z calcd for $C_{23}H_{25}NO_5$ 395.17327, found 395.1747



Bicyclo[4,4,0]alkenone (3.99n)

Bicyclo[4,4,0]alkenone (**3.99n**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **Me$_4$tBuXPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

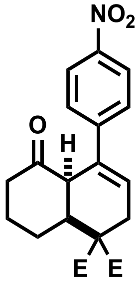
IR (neat, cm^{-1}) ν max 2981, 2941, 2227, 1750, 1731, 1605, 1255, 1181 ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.54 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 6.05 (ddd, J = 5.4 Hz, 2.6 Hz, 2.6 Hz, 1H), 4.28-4.12 (m, 4H), 3.94 (br, 1H), 3.10-3.02 (m, 2H), 2.85 (ddd, J = 19.6 Hz, 4.2 Hz, 2.6 Hz, 1H), 2.06-1.88 (m, 3H), 1..76-1.59 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 210.8 (C$_{quat}$), 170.9 (C$_{quat}$), 169.6 (C$_{quat}$), 144.5 (C$_{quat}$), 133.3 (C$_{quat}$), 132.2 (CHx2), 127.8 (CH), 127.7 (CHx2), 118.8 (C$_{quat}$), 111.2 (C$_{quat}$), 62.1 (CH$_2$), 62.1 (CH$_2$), 56.0 (C$_{quat}$), 52.6 (CH), 40.6 (CH), 39.9 (CH$_2$), 27.7 (CH$_2$), 25.7 (CH$_2$), 23.5 (CH$_2$), 14.2 (CH$_3$), 14.1 (CH$_3$) ; **HRMS (EI)** m/z calcd for $C_{23}H_{25}NO_5$ 395.17327, found 395.1722



Bicyclo[3.4.0]alkenone (3.98o)

Bicyclo[3,4,0]alkenone (**3.98o**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2943, 2867, 1733, 1662, 1521, 1343, 1195; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.10 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 1.6 Hz, 1H), 4.40-4.09 (m, 4H), 3.85 (d, J = 7.8 Hz, 1H), 3.54 (ddd, J = 17.6 Hz, 2.4 Hz, 2.4 Hz, 1H), 3.39 (ddd, J = 11.3 Hz, 7.5 Hz, 6.0 Hz, 1H), 3.03 (d, J = 17.7 Hz, 1H), 2.25-2.12 (m, 2H), 1.97-1.89 (m, 1H), 1.79-1.66 (m, 2H), 1.49-1.38 (m, 1H), 1.26 (t, J = 6.9 Hz, 6H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 209.0 (C$_{quat}$), 170.9 (C$_{quat}$), 169.4 (C$_{quat}$), 146.6 (C$_{quat}$), 142.9 (C$_{quat}$), 142.0 (C$_{quat}$), 129.6 (CHx2), 125.1 (CH), 123.5 (CHx2), 62.1 (C$_{quat}$), 62.0 (CH$_2$), 61.8 (CH$_2$), 56.6 (CH), 48.7 (CH), 41.2 (CH$_2$), 39.1 (CH$_2$), 24.3 (CH$_2$), 24.0 (CH$_2$), 14.2 (CH$_3$x2); **HRMS (EI)** m/z calcd for $C_{22}H_{25}NO_7$ [M$^+$] 415.1631, found 415.1651.

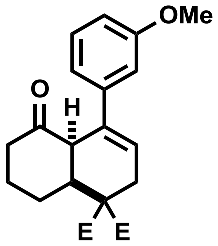


Bicyclo[4.4.0]alkenone (3.99o)

Bicyclo[4,4,0]alkenone (3.99o) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with Me$_4$**tBuXPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2981, 2942, 1729, 1596, 1345, 1262, 1181; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.11-8.06 (m, 2H), 7.37 (d, J = 8.9 Hz, 2H), 6.11 (ddd, J = 5.4 Hz, 2.6 Hz, 2.6 Hz, 1H), 4.28-4.12 (m, 4H), 3.96 (br, 1H), 3.12-3.09 (m, 2H), 2.87 (ddd, J = 19.6 Hz, 4.2 Hz, 2.6 Hz, 1H), 2.06-1.88 (m, 3H), 1..77-1.61 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 210.7 (C$_{quat}$), 169.6 (C$_{quat}$), 169.3 (C$_{quat}$), 147.0 (C$_{quat}$), 146.4 (C$_{quat}$), 133.0 (C$_{quat}$), 128.3 (CHx2), 127.8 (CH), 123.6 (CHx2), 62.1 (CH$_2$), 62.0 (CH$_2$), 55.9 (C$_{quat}$), 52.6 (CH), 40.6 (CH), 39.9 (CH$_2$), 27.6

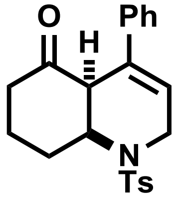
(CH_2), 25.7 (CH_2), 23.5 (CH_2), 14.1 (CH_3), 14.1 (CH_3); **HRMS (EI)** m/z calcd for $C_{22}H_{25}NO_7$ $[M^+]$ 415.1631, found 415.1650.

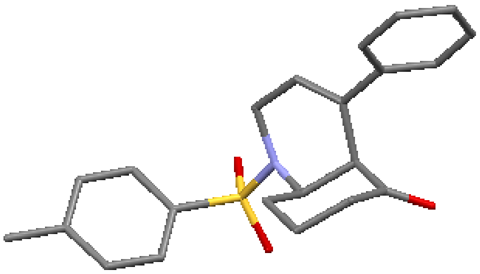


Bicyclo[4,4,0]alkenone (3.99p)

Bicyclo[4,4,0]alkenone was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **Me$_4$tBuXPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (ddd, J = 8.8 Hz, 7.7 Hz, 1.1 Hz, 1H), 6.80 (dd, J = 7.8 Hz, 1,2 Hz, 1H), 6.76-6.72 (m, 2H), 5.97 (dd, J = 5.4 Hz, 2.6 Hz, 2.6 Hz, 1H), 4.21 (dq, J = 16.4 Hz, 7.1 Hz, 2H), 4.21 (dq, J = 16.4 Hz, 7.1 Hz, 2H), 3.92 (br, 1H), 3.78 (s, 3H), 3.08-3.00 (m, 1H), 3,03-3,00 (m, 1H), 2.82 (ddd, J = 4.3 Hz, 2.6 Hz, 2.6 Hz, 1H), 2.12-1.97 (m, 3H), 1.69-1.59 (m, 3H), 1.25 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.25 (dd, J = 7.1 Hz, 7.1 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 221.7 (C_{quat}), 170.0 (C_{quat}), 169.7 (C_{quat}), 159.4 (C_{quat}), 141.4 (C_{quat}), 134.3 (C_{quat}), 129.3 (CH), 124.7 (CH), 119.0 (CH), 113.1 (CH), 112.8 (CH), 62.0 (CH_2),61.9 (CH_2), 56.2 (C_{quat}), 55.3 (CH_3), 53.0 (CH), 41.0 (CH), 39.9 (CH_2), 27.5 (CH_2), 26.2 (CH_2), 23.6 (CH_2), 14.2 (CH_3), 14.1 (CH_3), **; HRMS (EI)** m/z calcd for $C_{23}H_{28}O_6$ 400,1886, found 400,1873.

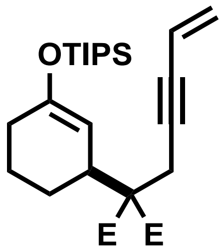




Bicyclo[4.4.0]decenone (3.99r)

Bicyclo[4,4,0]alkenone was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **JohnPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

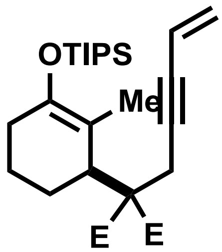
^{1}H NMR (400 MHz, CDCl$_3$) δ7.73 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.25-7.21 (m, 4H), 7.09 (dd, J = 8.4 Hz, 2.2 Hz, 1H), 5.89 (dt, J = 4.6 Hz, 2.4 Hz, 1H), 4,41-4.33 (m, 2H), 3.91 (ddd, J = 18.2 Hz, 2.4 Hz, 1.4 Hz, 2H), 3.64 (br, 1H), 2.43 (s, 3H), 1.99-1.85 (m,3H), 1.78-1.71(m, 1H), 1.54-1.47 (m, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ208.9 (C$_{quat}$), 143.9 (C$_{quat}$),138.8 (C$_{quat}$), 137.2 (C$_{quat}$), 134.5 (C$_{quat}$), (C$_{quat}$), 130.0 (CH), 128.6 (CH), 128.0 (CH), 127.2 (CH), 122.1 (CH), 54.4 ((CH), 54.0 (CH), 41.5 (CH$_2$), 39.2 (CH$_2$), 24.8 (CH$_2$), 22.6 (CH$_2$), 21.7 (CH$_3$) ; **HRMS (EI)** m/z calcd for $C_{22}H_{23}NO_3S$ [(M)$^+$] 381.1399, found 381.1375



Enyne (3.100a)

Silyl enol ether (**3.100a**) was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as a colorless oil in 88%.

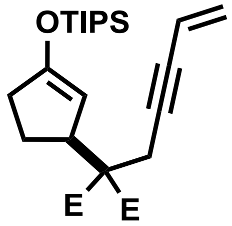
IR (neat, cm-1) ν max 2943, 2867, 1734, 1663, 1465, 1368, 1195, 916, 883, 684; **^{1}H NMR (300MHz , CDCl$_3$)** δ = 5.72 (tdd, *J* = 2.0, 11.0, 17.5 Hz, 1 H), 5.51 (dd, *J* = 2.3, 17.6 Hz, 1 H), 5.37 (dd, *J* = 2.3, 10.9 Hz, 1 H), 4.88 (s, 1 H), 4.24 - 4.12 (m, 4 H), 3.23 - 3.10 (m, 1 H), 2.92 (d, *J* = 2.0 Hz, 2 H), 2.17 - 1.77 (m, 4 H), 1.66 - 1.50 (m, 1 H), 1.43 - 1.02 (m, 4 H), 1.25 (dt, *J* = 5.0, 7.1 Hz, 6 H), 1.07 (s, 12 H), 1.05 (s, 6 H); **^{13}C NMR (75MHz, CDCl$_3$)** δ = 170.1 (C$_{quat}$), 170.0 (C$_{quat}$), 152.8 (C$_{quat}$), 126.3 (CH$_2$), 117.4 (CH), 103.9 (CH), 86.4 (C$_{quat}$), 81.8 (C$_{quat}$), 61.4 (CH$_2$), 61.3 (CH$_2$), 60.8 (C$_{quat}$), 38.9 (CH), 29.7 (CH$_2$), 24.3 (CH$_2$), 23.2 (CH$_2$), 22.6 (CH$_2$), 18.1 (CHx3), 14.2 (CH$_3$), 14.2 (CH$_3$), 12.6 (CH$_3$x6); **HRMS (EI)** m/z calcd for $C_{27}H_{44}O_5Si$ [M$^+$] 476.2958, found 476.2982.



Enyne (3.100b)

Silyl enol ether (**3.100b**) was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as a colorless oil in 72%.

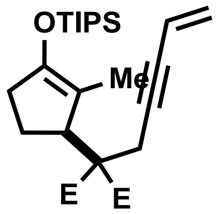
IR (neat, cm-1) ν max 2944, 2867, 1732, 1465, 1188, 924, 883, 681; **^{1}H NMR (300MHz, CDCl$_3$)** δ = 5.73 (tdd, *J* = 2.0, 10.9, 17.6 Hz, 1 H), 5.50 (dd, *J* = 2.4, 17.6 Hz, 1 H), 5.35 (dd, *J* = 2.4, 11.0 Hz, 1 H), 4.18 (qd, *J* = 7.1, 9.9 Hz, 4 H), 3.29 (t, *J* = 5.7 Hz, 1 H), 2.91 (dd, *J* = 2.0, 9.4 Hz, 2 H), 2.18 - 1.93 (m, 2 H), 1.63 (s, 3 H), 1.85 - 1.45 (m, 3 H), 1.26 (dt, *J* = 5.0, 7.1 Hz, 6 H), 1.18 - 0.94 (m, 22 H); **^{13}C NMR (75MHz, CDCl$_3$)** δ = 170.8 (C$_{quat}$), 170.7 (C$_{quat}$), 147.6 (C$_{quat}$), 126.0 (CH$_2$), 117.7 (CH), 110.8 (C$_{quat}$), 87.6 (C$_{quat}$), 81.4 (C$_{quat}$), 61.5 (CH$_2$), 61.5 (CH$_2$), 61.3 (CH), 43.2 (CH), 30.3 (CH$_2$), 25.8 (CH$_2$), 24.7 (CH$_2$), 21.4 (CH$_2$), 18.2 (CHx3), 15.4 (CH$_3$), 14.2 (CH$_3$), 14.0 (CH$_3$), 13.4 (CH$_3$x6); **HRMS (EI)** m/z calcd for $C_{28}H_{46}O_5Si$ [M$^+$] 490.3115, found 490.3126.



Enyne (3.100c) (Patrick Leveque master work)

Silyl enol ether (**3.100c**) was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as a colorless oil in 76% yield.

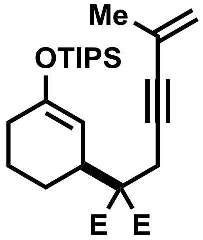
IR (neat, cm-1)) ν max 1737; **^{1}H NMR (500MHz, CDCl$_3$)** δ = 5.71 (tdd, *J* = 2.2, 11.1, 17.5 Hz, 1 H), 5.52 (dd, *J* = 2.2, 17.5 Hz, 1 H), 5.38 (dd, *J* = 2.2, 11.1 Hz, 1 H), 4.68 (q, *J* = 1.8 Hz, 1 H), 4.25 - 4.10 (m, 4 H), 2.89 (dq, *J* = 2.1, 17.5 Hz, 2 H), 2.32 - 2.20 (m, *J* = 1.9, 9.2 Hz, 2 H), 2.05 (dtd, *J* = 4.6, 8.8, 13.3 Hz, 1 H), 1.89 - 1.79 (m, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.20 - 1.10 (m, 3 H), 1.08 - 1.02 (m, 18 H); ^{13}C NMR **(126MHz, CDCl$_3$)** δ = 170.3 (C$_{quat}$), 170.3 (C$_{quat}$), 157.1 (C$_{quat}$), 126.3 (CH$_2$), 117.4 (CH), 102.7 (CH), 86.4 (C$_{quat}$), 81.6 (C$_{quat}$), 61.4 (2xCH$_2$), 60.9 (C$_{quat}$), 45.7 (CH), 33.1 (CH$_2$), 23.7 (CH$_2$), 23.3 (CH$_2$), 18.0 (9xCH$_3$), 14.2 (CH$_3$), 14.2 (CH$_3$), 12.5 (3xCH); **HRMS (EI)** m/z calcd for $C_{26}H_{42}O_5Si$ [M+] 462.2802, found 462.2802.



Enyne (3.100d) (Patrick Leveque master work)

Silyl enol ether (**3.100d**) was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as a colorless oil in 76% yield.

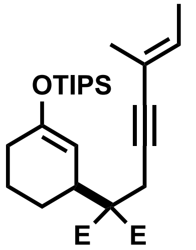
IR (neat, cm-1)) ν max 2943, 2868, 1738; **^{1}H NMR (400MHz, CDCl$_3$)** δ = 5.72 (tdd, *J* = 2.3, 11.0, 17.5 Hz, 1 H), 5.51 (dd, *J* = 2.3, 17.5 Hz, 2 H), 5.37 (dd, *J* = 2.3, 11.0 Hz, 2 H), 4.26 - 4.10 (m, 4 H), 3.58 - 3.50 (m, 1 H), 3.03 (dd, *J* = 2.2, 17.3 Hz, 1 H), 2.85 (dd, *J* = 2.1, 17.3 Hz, 1 H), 1.54 (s, 3 H), 1.26 (dt, *J* = 3.5, 7.1 Hz, 16 H), 1.07 (s, 12 H), 1.06 (s, 6 H); **^{13}C NMR (101MHz, CDCl$_3$)** δ = 170.4 (C$_{quat}$), 170.1 (C$_{quat}$), 150.7 (C$_{quat}$), 126.0 (CH2), 117.4 (CH), 111.6 (C$_{quat}$), 86.9 (C$_{quat}$), 81.3 (C$_{quat}$), 61.3 (CH$_2$), 61.3 (CH$_2$), 61.0 (C$_{quat}$), 49.0 (CH), 32.2 (CH$_2$), 23.6 (CH$_2$), 23.3 (CH$_2$), 17.9 (CH$_3$x3), 17.9 (CH$_3$x3), 14.1 (CH$_3$), 14.0 (CH$_3$), 12.8 (CHx3), 11.8 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{27}H_{44}O_5Si$ [M+] 476.2958, found 476.2959.



Enyne (3.100e) (Patrick Leveque master work)

Prepared according to general procedure G from the corresponding terminal alkyne and 2-bromoprop-1-ene in 78% yield as a clear oil.

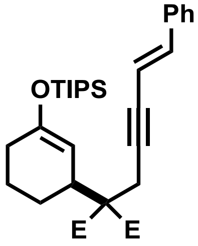
IR (neat, cm-1) ν max 2943, 2867, 1734, 1664, 1464, 1371, 1195, 883, 685; **^{1}H NMR (400MHz, CDCl$_3$)** δ = 5.17 - 5.14 (m, 1 H), 5.12 (dq, *J* = 1.7 Hz, 1 H), 4.87 (s, 1 H), 4.26 - 4.10 (m, 4 H), 3.20 - 3.13 (m, 1 H), 2.91 (d, *J* = 1.7 Hz, 2 H), 2.15 - 2.02 (m, 1 H), 2.01 - 1.91 (m, 1 H), 1.90 - 1.79 (m, 2 H), 1.83 - 1.79 (m, 3 H), 1.67-1.50 (m, 1 H), 1.44 - 1.31 (m, 1 H), 1.25 (q, *J* = 7.2 Hz, 6 H), 1.19 - 1.09 (m, 3 H), 1.07 (s, 12 H), 1.05 (s, 6 H); **^{13}C NMR (101MHz, CDCl$_3$)** δ = 170.0 (C$_{quat}$), 169.9 (C$_{quat}$), 152.7 (C$_{quat}$), 126.9 (C$_{quat}$), 120.8 (CH2), 103.8 (CH), 84.7 (C), 84.2 (C$_{quat}$), 61.3 (CH$_2$), 61.2 (CH$_2$), 60.7 (C), 38.8 (CH), 29.6 (CH_2), 24.2 (CH_2), 23.5 (CH_3), 23.0 (CH_2), 22.5 (CH_2), 18.0 (CH_3x6), 14.1 (CH_3), 14.0 (CH_3), 12.5 (CHx3); **HRMS (EI)** m/z calcd for $C_{28}H_{46}O_5Si$ [M+] 490.3115, found 490.3134.



Enyne (3.100f) (Patrick Leveque master work)

Silyl enol ether (**3.100f**) was prepared according to the **general procedure F** Sonogashira reaction from silyl enol ether (**3.96b**) and (E)-2-bromobut-2-ene in 52% yield as a clear oil.

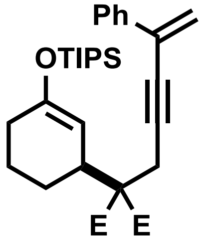
IR (neat, cm-1) ν max 2943, 2867, 1734, 1663, 1465, 1366, 1223, 1194, 884, 680; **^{1}H NMR (300MHz, $CDCl_3$)** δ = 5.75 (qq, *J* = 1.3, 7.0 Hz, 1 H), 4.86 (s, 1 H), 4.22 - 4.08 (m, 4 H), 3.19 - 3.10 (m, 1 H), 2.87 (s, 2 H), 2.12 - 1.98 (m, 1 H), 1.98 - 1.92 (m, 1 H), 1.92 - 1.74 (m, *J* = 4.8 Hz, 2 H), 1.67 (t, *J* = 1.3 Hz, 3 H), 1.60 (dd, *J* = 0.9, 7.0 Hz, 3 H), 1.65 - 1.27 (m, 2 H), 1.22 (dt, *J* = 5.5, 7.1 Hz, 6 H), 1.04 (s, 12 H), 1.02 (s, 6 H), 1.16 - 1.00 (m, 3 H); **^{13}C NMR (75MHz, $CDCl_3$)** δ = 170.0 (C_{quat}), 169.9 (C_{quat}), 152.4 (C_{quat}), 131.2 (CH), 118.4 (C_{quat}), 103.9 (CH), 86.0 (C_{quat}), 81.3 (C_{quat}), 61.1 (CH_2), 61.0 (CH_2), 60.7 (C_{quat}), 38.6 (CH), 29.6 (CH_2), 24.1 (CH_2), 23.0 (CH_2), 22.4 (CH_2), 17.9 (CHx3), 16.9 (CH_3), 14.0 (CH_3), 14.0 (CH_3), 13.8 (CH_3), 12.5 (CH_3x6); **HRMS (EI)** m/z calcd for $C_{29}H_{48}O_5Si$ [M^+] 504.3271, found 552.3256.



Enyne (3.100g) (Patrick Leveque master work)

Silyl enol ether (**3.100g**) was prepared according to the **general procedure F** Sonogashira reaction from silyl enol ether (**3.96b**) and (E)-(2-iodovinyl)benzene in 89% yield as a clear oil.

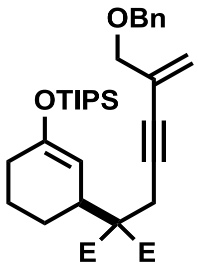
IR (neat, cm-1) ν max 2943, 2866, 1731, 1661, 1463, 1367, 1195, 748, 690; **^{1}H NMR (400MHz, CDCl$_3$)** δ = 7.36 - 7.23 (m, 5 H), 6.82 (d, *J* = 16.3 Hz, 1 H), 6.09 (td, *J* = 1.9, 16.2 Hz, 1 H), 4.91 (s, 1 H), 4.27 - 4.14 (m, 4 H), 3.21 (d, *J* = 9.2 Hz, 1 H), 2.99 (d, *J* = 1.7 Hz, 2 H), 2.18 - 1.79 (m, 4 H), 1.68 - 1.49 (m, 1 H), 1.45 - 1.33 (m, *J* = 11.9 Hz, 1 H), 1.26 (q, *J* = 7.3 Hz, 6 H), 1.23 - 1.10 (m, 3 H), 1.08 (s, 12 H), 1.06 (s, 6 H); **^{13}C NMR (101MHz, CDCl$_3$)** δ = 170.0 (C$_{quat}$), 169.9 (C$_{quat}$), 152.7 (C$_{quat}$), 140.6 (CH), 136.4 (C$_{quat}$), 128.6 (CHx2), 128.3 (CH), 126.1 (CHx2), 108.5 (CH), 103.8 (CH), 88.0 (C$_{quat}$), 82.1 (C$_{quat}$), 61.3 (CH$_2$), 61.3 (CH$_2$), 60.8 (C$_{quat}$), 38.9 (CH), 29.7 (CH$_2$), 24.2 (CH$_2$), 23.4 (CH$_2$), 22.5 (CH$_2$), 18.0 (CHx3), 14.1 (CH$_3$), 14.1 (CH$_3$), 12.5 (CH$_3$x6); **HRMS (EI)** m/z calcd for $C_{33}H_{48}O_5Si$ [M$^+$] 552.3271, found 552.3260.



Enyne (3.100h) (Patrick Leveque master work)

Silyl enol ether (**3.100h**) was prepared according to the **general procedure F** Sonogashira reaction from silyl enol ether (**3.96b**) and α-bromostyrene in 53% yield as a clear oil.

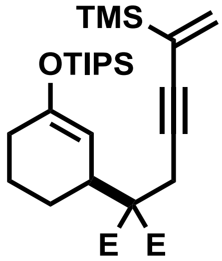
IR (neat, cm-1) ν max 2443, 2866, 1731, 1195, 880, 675; **^{1}H NMR (400MHz ,CDCl$_3$)** δ = 7.62 - 7.58 (m, 2 H), 7.35 - 7.27 (m, 3 H), 5.84 (d, *J* = 1.0 Hz, 1 H), 5.55 (d, *J* = 0.7 Hz, 1 H), 4.91 (s, 1 H), 4.24 - 4.14 (m, 6 H), 3.28 - 3.19 (m, 1 H), 3.04 (d, *J* = 2.2 Hz, 2 H), 2.17 - 2.03 (m, 1 H), 2.01 - 1.78 (m, 3 H), 1.55 (s, 1 H), 1.42 (ddt, *J* = 2.4, 10.2, 12.5 Hz, 1 H), 1.24 (dt, *J* = 4.0, 7.1 Hz, 6 H), 1.19 - 1.09 (m, 3 H), 1.08 - 1.06 (m, 12 H), 1.06 - 1.04 (m, 6 H); **^{13}C NMR (101MHz, CDCl$_3$)** δ = 170.0 (C$_{quat}$), 169.9 (C$_{quat}$), 152.7 (C$_{quat}$), 137.4 (C$_{quat}$), 130.6 (C$_{quat}$), 128.2 (CHx2), 128.1 (CH), 126.0 (CHx2), 119.9 (CH$_2$), 103.8 (CH), 87.2 (C$_{quat}$), 82.1 (C$_{quat}$), 61.4 (CH$_2$), 61.3 (CH$_2$), 60.8 (C$_{quat}$), 39.0 (CH), 29.6 (CH$_2$), 24.3 (CH$_2$), 23.3 (CH$_2$), 22.5 (CH$_2$), 18.0 (CHx3), 14.0 (CH$_3$), 14.0 (CH$_3$), 12.5 (CH$_3$x6); **HRMS (EI)** m/z calcd for $C_{33}H_{48}O_5Si$ [M$^+$] 552.3271, found 552.3245.



Enyne (3.100i)

Silyl enol ether (**3.100i**) was prepared according to the **general procedure F** Sonogashira reaction from silyl enol ether (**3.96b**) and ((2-bromoallyloxy)methyl)benzene in 57% yield as a clear oil.

IR (neat, cm-1) ν max 2943, 2866, 1734, 1662, 1368 1221, 1194, 1096, 881, 752, 681; **^{1}H NMR (400MHz, CDCl$_3$)** δ = 7.40 - 7.24 (m, 5 H), 5.49 (q, *J* = 1.7 Hz, 1 H), 5.43 - 5.40 (m, 1 H), 4.86 (s, 1 H), 4.53 (s, 2 H), 4.30 - 4.09 (m, 4 H), 3.96 (t, *J* = 1.3 Hz, 2 H), 3.22 - 3.10 (m, 1 H), 2.94 (d, *J* = 3.5 Hz, 2 H), 2.14 - 2.02 (m, 1 H), 1.95 (td, *J* = 2.8, 17.0 Hz, 1 H), 1.91 - 1.77 (m, 2 H), 1.61 - 1.49 (m, 1 H), 1.45 - 1.30 (m, 1 H), 1.23 (dt, *J* = 4.5, 7.1 Hz, 6 H), 1.19 - 1.09 (m, 3 H), 1.07 (s, 12 H), 1.06 (s, 6 H); **^{13}C NMR (101MHz, CDCl$_3$)** δ = 170.0 (C), 169.8 (C), 152.7 (C), 138.1 (C), 128.4 (C), 128.4 (CHx2), 127.7 (CHx2), 127.6 (CH), 121.0 (CH$_2$), 103.7 (CH), 86.7 (C), 81.3 (C), 72.2 (CH$_2$), 72.1 (CH$_2$), 61.3 (CH), 61.2 (CH$_2$), 60.7 (C), 38.9 (CH), 29.6 (CH$_2$), 24.2 (CH$_2$), 23.1 (CH$_2$), 22.5 (CH$_2$), 18.0 (CHx3), 14.1 (CH$_3$), 14.0 (CH$_3$), 12.5 (CH$_3$x6); **HRMS (EI)** m/z calcd for $C_{35}H_{42}O_6Si$ [(M-CH$_2$Ph)$^+$] 505.2985, found 505.2977.

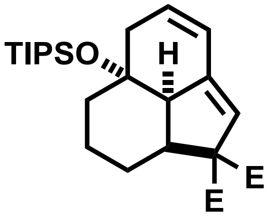


Enyne (3.100j) (Patrick Leveque master work)

Enyne was prepared according to the **general procedure F** Sonogashira reaction and isolated as a clear oil.

IR (neat, cm-1) 2945, 2866, 1734, 1249, 1197, 841; **^{1}H NMR (400MHz ,CDCl$_3$)** δ = 5.97 (d, *J* = 3.4 Hz, 1 H), 5.61 (d, *J* = 3.5 Hz, 1 H), 4.90 (s, 1 H), 4.22 - 4.11 (m, 4 H), 3.24 - 3.14 (m, 1 H), 3.00 (d, *J* = 5.4 Hz, 2 H), 2.14 - 1.78 (m, 4 H), 1.63 - 1.50 (m, 1 H), 1.44 - 1.32 (m, 1 H), 1.24 (q, *J* = 7.2 Hz, 6

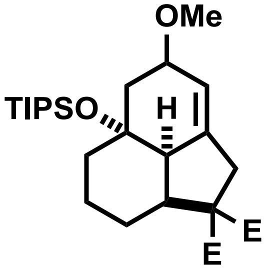
H), 1.20 - 1.09 (m, 3 H), 1.07 (s, 12 H), 1.05 (s, 6 H), 0.12 (s, 9 H); **^{13}C NMR (101MHz, CDCl$_3$)** δ = 170.1 (C_{quat}), 169.9 (C_{quat}), 152.4 (C_{quat}), 134.7 (C_{quat}), 133.4 (CH2), 104.1 (CH), 89.0 (C_{quat}), 84.3 (C_{quat}), 61.2 (CH_2), 61.1 (CH_2), 60.7 (C_{quat}), 38.5 (CH), 29.6 (CH_2), 24.1 (CH_2), 23.9 (CH_2), 22.5 (CH_2), 18.0 (CH3x6), 14.1 (CH_3), 14.1 (CH_3), 12.5 (CHx3), -2.2 (CH_3x3); **HRMS (EI)** m/z calcd for $C_{25}H_{39}O_5Si$ [M^+] 548.3353, found 548.3350.



Tricycle (3.101a)

Tricycle (**3.101a**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm-1) ν max 2940, 2865, 1733, 1461, 1221, 1058, 882, 675; **mp (°C)** 100.4-102.1; **^{1}H NMR (300MHz, C$_6$D$_6$)** δ = 6.11 (dd, *J* = 3.0, 9.7 Hz, 1 H), 6.04 (d, *J* = 3.0 Hz, 1 H), 5.55 (ddd, *J* = 2.2, 6.1, 9.7 Hz, 1 H), 4.15 - 3.90 (m, 3 H), 3.80 (m, 2 H), 3.60 (br. s., 1 H), 2.44 (d, *J* = 17.4 Hz, 1 H), 2.06 (dd, *J* = 6.1, 17.2 Hz, 1 H), 2.14 - 1.91 (m, 1 H), 1.75 - 1.63 (m, 1 H), 1.53 - 1.32 (m, 4 H), 1.22 - 1.00 (m, 21 H), 0.90 (td, *J* = 7.1, 20.0 Hz, 6 H); **^{13}C NMR (75MHz, C$_6$D$_6$)** δ = 169.4 (C_{quat}), 168.6 (C_{quat}), 144.2 (C_{quat}), 131.0 (CH), 122.6 (CH), 122.4 (CH), 72.0 (C_{quat}), 69.4 (C_{quat}), 60.8 (CH_2), 60.5 (CH_2), 52.2 (CH), 43.1 (CH), 41.2 (CH_2), 34.4 (CH_2), 23.4 (CH_2), 19.4 (CH_2), 18.4 (CHx3), 13.8 (CH_3), 13.6 (CH_3), 13.6 (CH_3x6); **HRMS (EI)** m/z calcd for $C_{24}H_{37}O_5Si$ [$(M-_iPr)^+$] 433.2410, found 433.2416.

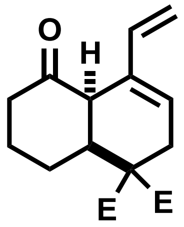


Tricycle (3.X5)

Tricycle (**3.X5**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and MeOH as solvent and isolated as a 7:13 mixture of diasterioisomers as clear oils. Stereochemistry could not be determined by 2D-NMR.

Major: IR (neat, cm-1) 2942, 2866, 1734, 1462, 1247, 1152, 1093, 883, 676; **^{1}H NMR (400MHz, $CDCl_3$)** δ = 5.62 (br. s., 1 H), 4.31 - 4.05 (m, 4 H), 3.85 (ddd, *J* = 2.0, 3.7 Hz, 1 H), 3.33 (s, 3 H), 3.28 (ddd, *J* = 2.1 Hz, 1 H), 3.03 (ddd, *J* = 5.8, 13.0 Hz, 1 H), 2.88 (d, *J* = 18.7 Hz, 1 H), 2.66 (br. s., 1 H), 2.11 (d, *J* = 13.8 Hz, 1 H), 1.91 - 1.77 (m, 1 H), 1.76 - 1.63 (m, 2 H), 1.44 - 1.29 (m, 3 H), 1.24 (dt, *J* = 7.1 Hz, 6 H), 1.13 - 1.06 (m, 21 H), 0.80 (dddd, *J* = 2.7, 13.0 Hz, 1 H); **^{13}C NMR (101MHz, $CDCl_3$)** □ = 171.8 (C_{quat}), 169.8 (C_{quat}), 142.9 (C_{quat}), 117.6 (CH), 76.4 (CH), 72.3 (C_{quat}), 62.3(C_{quat}), 61.4 (CH_2), 61.4 (CH_2), 56.6 (CH), 52.1 (CH), 42.4 (CH), 40.3 (CH_2), 35.6 (CH_2), 32.9 (CH_2), 23.4 (CH_2), 20.0 (CH_2), 18.5 (CHx3), 14.1 (CH_3), 14.0 (CH_3), 13.7 (CH_3x6); **HRMS (EI)** m/z calcd for C25H41O6Si $[(M-_iPr)^+]$ 465.2672, found 465.2716.

Minor: IR (neat, cm-1) 2941, 2866, 1735, 1465, 1366, 1248, 1085, 883, 679; **^{1}H NMR (300MHz, $CDCl_3$)** δ = 5.56 (br. s., 1 H), 4.32 - 4.05 (m, 4 H), 3.91 (br. s., 1 H), 3.36 (s, 3 H), 3.34 - 3.23 (m, 1 H), 3.00 (ddd, *J* = 6.0, 12.3 Hz, 1 H), 2.89 (d, *J* = 18.9 Hz, 1 H), 2.81 (br. s., 1 H), 2.18 (dd, *J* = 6.2, 11.8 Hz, 1 H), 1.85 - 1.59 (m, 2 H), 1.23 (dt, *J* = 7.1 Hz, 6 H), 1.51 - 1.02 (m, 7 H), 1.09 (s, 18 H), 0.73 (dddd, *J* = 3.2, 13.1 Hz, 1 H); **^{13}C NMR (75MHz, $CDCl_3$)** δ = 171.6 (C_{quat}), 169.9 (C_{quat}), 142.7 (C_{quat}), 117.8 (CH), 77.6 (CH), 73.8 (C_{quat}), 62.2 (C_{quat}), 61.4 (CH_2x2), 55.6 (CH_3), 51.8 (CH), 42.6 (CH_2), 41.7 (CH), 35.4 (CH_2), 32.8 (CH_2), 23.2 (CH_2), 19.5 (CH_2), 18.5 (CHx3), 14.1 (CH_3), 14.0 (CH_3), 13.6 (CH_3x6); **HRMS (EI) m/z calcd for** C25H41O6Si $[(M-_iPr)^+]$ 465.2672, found 465.2696.

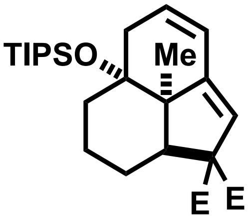


Diene (3.102a) (Patrick Leveque master work)

Diene (**3.102a**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **Me$_4$tBuXPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm-1) 2927, 2849, 1733, 1463, 1444, 1236, 1180, 1051, 862, 736; **^{1}H NMR (400MHz ,$CDCl_3$)** δ = 6.12 (dd, *J* = 11.3, 17.7 Hz, 1 H), 5.85 (td, *J* = 2.4, 5.2 Hz, 1 H), 5.14 (d, *J* = 17.7 Hz, 1

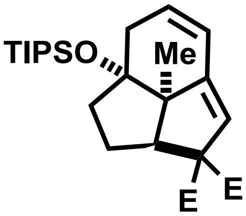
H), 4.90 (d, *J* = 11.3 Hz, 1 H), 4.26 - 4.08 (m, 4 H), 3.49 (br. s., 1 H), 2.97 - 2.87 (m, 2 H), 2.74 (d, *J* = 20.0 Hz, 1 H), 2.34 - 2.16 (m, 2 H), 2.05 - 1.97 (m, 1 H), 1.70 - 1.48 (m, 3 H), 1.22 (q, *J* = 7.1 Hz, 6 H); **^{13}C NMR (101MHz ,CDCl$_3$)** δ = 213.0 (C$_{quat}$), 169.8 (C$_{quat}$), 169.4 (C$_{quat}$), 136.8 (CH), 131.8 (C$_{quat}$), 125.6 (CH), 114.5 (CH$_2$), 61.9 (CH$_2$), 61.8 (CH$_2$), 56.2 (C$_{quat}$), 52.0 (CH), 41.0 (CH), 39.5 (CH$_2$), 27.3 (CH$_2$), 26.0 (CH$_2$), 23.5 (CH$_2$), 14.0 (CH$_3$), 14.0 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{18}H_{24}O_5$ [M$^+$] 320.1624, found 320.1604.



Tricycle (3.101b)

Tricycle (**3.101b**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **JohnPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

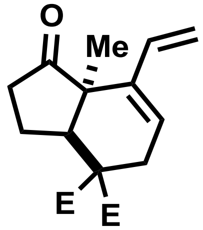
IR (neat, cm-1) ν max 2943, 2867, 1733, 1456, 1188, 1095, 1058, 882, 715, 672; **mp (°C)** 71.8-73.2; **^{1}H NMR (300MHz, CDCl$_3$)** δ = 6.21 (dd, *J* = 2.7, 9.7 Hz, 1 H), 5.75 (ddd, *J* = 2.4, 5.9, 9.7 Hz, 1 H), 5.64 (s, 1 H), 4.31 - 4.05 (m, 4 H), 3.07 (dd, *J* = 6.5, 10.8 Hz, 1 H), 2.59 (td, *J* = 2.2, 17.8 Hz, 1 H), 2.08 (dd, *J* = 6.1, 18.1 Hz, 1 H), 1.83 - 1.55 (m, 2 H), 1.44 (dd, *J* = 3.7, 8.0 Hz, 2 H), 1.25 (dt, *J* = 6.0, 7.1 Hz, 6 H), 1.35 - 1.02 (m, 26 H); **^{13}C NMR (75MHz, CDCl$_3$)** δ = 171.3 (C$_{quat}$), 170.5 (C$_{quat}$), 149.6 (C$_{quat}$), 129.9 (CH), 122.2 (CH), 120.7 (CH), 75.5 (C$_{quat}$), 70.2 (C$_{quat}$), 61.7 (CH$_2$), 61.6 (CH$_2$), 52.9 (C$_{quat}$), 48.5 (CH), 39.7 (CH$_2$), 35.1 (CH$_2$), 25.7 (CH$_2$), 24.3 (CH$_3$), 18.8 (CHx1), 18.7 (CH$_2$), 18.7 (CHx2), 14.3 (CH$_3$), 14.1 (CH$_3$), 13.9 (CH$_3$x6); **HRMS (EI)** m/z calcd for $C_{28}H_{46}O_5Si$ [M$^+$] 490.3115, found 490.3147.



Tricycle (3.101d) (Patrick Leveque master work)

Tricycle (**3.101d**) prepared according to the **general procedure G** Gold-Catalyzed Carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as white powder.

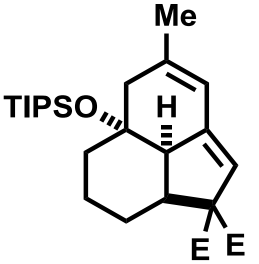
IR (neat, cm-1) ν max 2945, 2867, 1734, 1325, 1210, 1140, 1056, 916; **mp (°C)** 63.4-64.8; **^{1}H NMR (400MHz ,CDCl$_3$) ^{1}H NMR (400MHz, CDCl$_3$)** δ = 6.16 (dd, *J* = 1.5, 9.8 Hz, 1 H), 5.70 (ddd, *J* = 2.7, 5.2, 9.8 Hz, 1 H), 5.55 (s, 1 H), 4.28 - 4.08 (m, 4 H), 3.22 (dd, *J* = 2.7, 10.8 Hz, 1 H), 2.50 (ddd, *J* = 1.5, 5.2, 18.5 Hz, 1 H), 2.39 (dtd, *J* = 0.6, 2.7, 18.7 Hz, 1 H), 2.22 - 2.06 (m, 1 H), 1.59 (s, 2 H), 1.28 (s, 6 H), 1.08 (s, 18 H), 1.23 - 1.05 (m, 7 H); **^{13}C NMR (101MHz , CDCl$_3$)** δ = 170.9 (C$_{quat}$), 170.2 (C$_{quat}$), 151.1 (C$_{quat}$), 129.5 (CH), 121.1 (CH), 120.4 (CH), 83.7 (C$_{quat}$), 69.7 (C$_{quat}$), 61.5 (C$_{quat}$), 61.4 (CH$_2$), 61.2 (CH$_2$), 51.7 (CH), 37.0 (CH$_2$), 35.6 (CH$_2$), 25.8 (CH$_2$), 18.4 (CHx3), 17.7 (CH$_3$), 14.2 (CH$_3$), 14.1 (CH$_3$), 13.5 (CH$_3$x6); **HRMS (EI)** m/z calcd for $C_{24}H_{37}O_5Si$ $[(M\text{-}{}_{i}Pr)^+]$ 433.2410, found 433.2423.



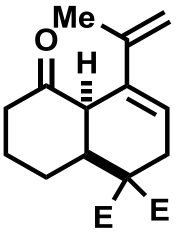
Diene (3.102d) (Patrick Leveque master work)

Diene (**3.102c**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **Me$_4$tBuXPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

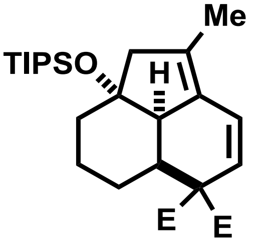
IR (neat, cm-1) ν max 2983, 2934, 1735, 1241, 1174, 1095, 1059; **^{1}H NMR (300MHz ,CDCl$_3$)** δ = 6.26 (dd, *J* = 10.8, 17.0 Hz, 1 H), 5.95 (dd, *J* = 2.3, 5.8 Hz, 1 H), 5.33 (d, *J* = 17.2 Hz, 1 H), 4.96 (d, *J* = 11.2 Hz, 1 H), 4.30 - 4.04 (m, 4 H), 3.11 - 2.94 (m, 2 H), 2.53 (d, *J* = 19.3 Hz, 1 H), 2.46 - 2.12 (m, 3 H), 1.72 - 1.54 (m, 1 H), 1.26 (dt, *J* = 5.9, 7.1 Hz, 6 H), 1.14 (s, 3 H); **^{13}C NMR (75MHz ,CDCl$_3$)** δ = 217.0 (C$_{quat}$), 170.1 (C$_{quat}$), 169.8 (C$_{quat}$), 134.5 (CH), 134.2 (C$_{quat}$), 121.9 (CH), 114.7 (CH$_2$), 61.6 (CH$_2$x2), 54.0 (C$_{quat}$), 52.5 (C$_{quat}$), 46.5 (CH), 35.0 (CH$_2$), 26.9 (CH$_2$), 22.2 (CH$_3$), 21.8 (CH$_2$), 14.0 (CH$_3$), 13.9 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{18}H_{24}O_5$ [M+] 320.1624, found 320.1623.



3.101e



3.102e



3.104e

Polycyclic compound mixture of dienes (3.101e), (3.102e) and (3.104e)

Mixture was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **Me$_{4t}$BuXPhos**AuNCMeSbF$_6$ **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil. Characterized as a mixture.

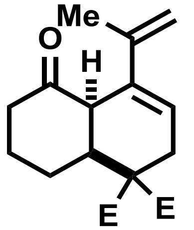
Mixture: IR (neat, cm-1) ν max 2940, 2866, 1739, 1733, 1460, 1242, 1058, 882, 680; **HRMS (EI)** m/z calcd for C25H39O5Si [(M-$_i$Pr)$^+$] 447.2567, found 447.2572.

Major: ^{1}H NMR (500MHz, CDCl$_3$) δ = 5.96 (d, *J* = 1.8 Hz, 1 H), 4.80 - 4.68 (br. s., 2 H), 4.33 - 4.02 (m, 4 H), 3.31 (d, *J* = 19.5 Hz, 1 H), 3.02 (td, *J* = 5.7, 13.0 Hz, 1 H), 2.93 (d, *J* = 19.6 Hz, 1 H), 2.87 (br. s., 1 H), 2.49 (d, *J* = 13.7 Hz, 1 H), 2.34 (d, *J* = 13.7 Hz, 1 H), 1.24 (s, 6 H), 1.11 - 1.08 (m, 18 H), 1.85 - 0.68 (m, 9 H); ^{13}C **NMR (126MHz, CDCl$_3$)** □ = 171.6 (C$_{quat}$), 169.8 (C$_{quat}$), 143.6 (C$_{quat}$), 143.1 (C$_{quat}$), 122.2 (CH), 110.4 (CH$_2$), 73.2 (C$_{quat}$), 62.5 (C$_{quat}$), 61.4 (CH$_2$), 61.3 (CH$_2$), 52.2 (CH), 45.4 (CH$_2$), 42.1 (CH), 35.6 (CH$_2$), 32.2 (CH$_2$), 23.2 (CH$_2$), 19.6 (CH$_2$), 18.5 (CHx2), 18.4 (CH), 14.1 (CH$_3$), 14.1 (CH$_3$), 13.6 (CH$_3$x6).

Minor: ^{1}H NMR (500MHz, CDCl$_3$) δ = 6.44 (d, *J* = 9.8 Hz, 1 H), 5.89 (d, *J* = 9.8 Hz, 1 H), 4.31 - 4.03 (m, 4 H), 3.28 - 3.21 (m, 0 H), 2.76 (dtd, *J* = 0.9, 4.8, 12.9 Hz, 1 H), 2.65 (d, *J* = 15.2 Hz, 1 H), 2.09 (d, *J* = 15.2 Hz, 1 H), 1.71 (s, 3 H), 1.29 - 1.17 (m, 6 H), 1.13 - 1.04 (m, 18 H), 1.83 - 0.68 (m, 9 H); **^{13}C NMR (126MHz, CDCl$_3$)** □ = 170.8 (C$_{quat}$), 169.3 (C$_{quat}$), 133.9 (C$_{quat}$), 129.8 (C$_{quat}$), 122.6 (CH), 122.5 (CH), 80.3 (C$_{quat}$), 61.3 (CH$_2$), 61.2 (CH$_2$), 59.5 (C$_{quat}$), 52.2 (CH$_2$), 49.3 (CH), 36.2 (CH$_2$), 34.1 (CH), 24.4 (CH$_2$), 21.0 (CH$_2$), 18.4 (CHx$_3$), 14.1 (CH$_3$), 14.1 (CH$_3$), 14.0 (CH$_3$), 13.2 (CH$_3$x6).

Trace: ^{1}H NMR (500MHz ,CDCl$_3$) δ = 6.00 (s, 1 H), 5.49 (d, *J* = 2.8 Hz, 1 H), 4.30 - 4.04 (m, 4 H), 3.27 - 3.22 (m, 1 H), 3.16 - 3.12 (m, 1 H), 2.49 (d, *J* = 16.9 Hz, 1 H), 2.04 (d, *J* = 16.9 Hz, 1 H), 1.79 (s, 3 H), 1.29 - 1.18 (m, 6 H), 1.12 - 1.07 (m, 18 H), 1.83 - 0.68 (m, 9 H); **^{13}C NMR (126MHz, CDCl$_3$)** □ = 170.4 (C$_{quat}$), 169.3 (C$_{quat}$), 145.0 (C$_{quat}$), 140.9 (C$_{quat}$), 118.6 (CH), 118.2 (CH), 72.2

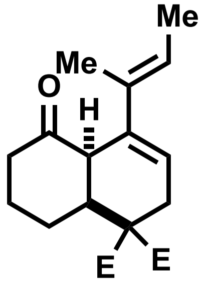
(C_{quat}), 69.4 (C_{quat}), 61.0 (CH_2), 60.9 (CH_2), 51.4 (CH), 46.5 (CH_2), 42.4 (CH), 34.4 (CH_2), 23.9 (CH_3), 23.2 (CH_2), 19.1 (CH_2), 18.5 (CHx3), 14.1 (CH_3), 14.1 (CH_3), 13.7 (CH_3x6).



Diene (3.102e) (Patrick Leveque master work)

Diene (**3.102e**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **Me$_{4t}$BuXPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

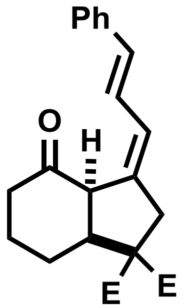
IR (neat, cm-1) ν max 2979, 2942, 2870, 1733, 1714, 1445, 1367, 1255, 1180, 898; **^{1}H NMR (300MHz, CDCl$_3$)** δ = 5.80 (td, *J* = 2.6, 5.3 Hz, 1 H), 4.80 (s, 2 H), 4.22 - 4.10 (m, 4 H), 3.61 - 3.51 (m, *J* = 1.5 Hz, 1 H), 2.95 - 2.84 (m, 2 H), 2.71 (td, *J* = 3.3, 19.5 Hz, 1 H), 2.31 - 2.07 (m, 2 H), 2.07 - 1.88 (m, 1 H), 1.79 (s, 3 H), 1.70 - 1.49 (m, 3 H), 1.21 (dt, *J* = 3.4, 7.1 Hz, 6 H); **^{13}C NMR (75MHz, CDCl$_3$)** δ = 212.8 (C_{quat}), 169.8 (C_{quat}), 169.5 (C_{quat}), 143.4 (C_{quat}), 135.2 (C_{quat}), 122.4 (CH), 114.0 (CH_2), 61.8 (CH_2), 61.7 (CH_2), 56.1 (C_{quat}), 52.4 (CH), 41.0 (CH), 39.4 (CH_2), 27.1 (CH_2), 26.2 (CH_2), 23.5 (CH_2), 21.6 (CH_3), 14.0 (CH_3), 13.9 (CH_3); **HRMS (EI)** m/z calcd for $C_{19}H_{26}O_5$ [M+] 334.1780, found 334.1781.



Diene (3.102f) (Patrick Leveque master work)

Diene (**3.102f**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **Me$_4$tBuXPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

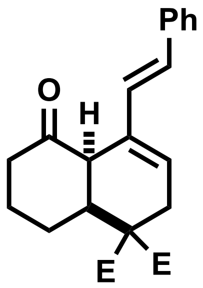
IR (neat, cm-1) ν max 2981, 2940, 2866, 1733, 1713, 1445, 1235, 1180, 1049, 916, 733; **^{1}H NMR (300MHz, CDCl$_3$)** δ = 5.64 (td, *J* = 2.4, 5.1 Hz, 1 H), 5.35 (q, *J* = 6.7 Hz, 1 H), 4.22 - 4.10 (m, 4 H), 3.57 (br. s., 1 H), 2.92 - 2.81 (m, 2 H), 2.67 (td, *J* = 2.8, 19.2 Hz, 1 H), 2.27 - 2.07 (m, 2 H), 2.05 - 1.90 (m, 1 H), 1.63 (d, *J* = 0.7 Hz, 3 H), 1.54 (d, *J* = 6.7 Hz, 3 H), 1.66 - 1.50 (m, 3 H), 1.21 (ddt, *J* = 0.7, 2.4, 7.1 Hz, 6 H); **^{13}C NMR (75MHz ,CDCl$_3$)** δ = 212.4 (C$_{quat}$), 169.9 (C$_{quat}$), 169.6 (C$_{quat}$), 137.3 (C$_{quat}$), 135.9 (C$_{quat}$), 122.8 (CH), 120.5 (CH), 61.7 (CH$_2$), 61.6 (CH$_2$), 56.1 (C$_{quat}$), 52.3 (CH), 40.7 (CH), 39.5 (CH$_2$), 26.9 (CH$_2$), 26.0 (CH$_2$), 23.5 (CH$_2$), 15.0 (CH$_3$), 14.0 (CH$_3$), 13.9 (CH$_3$), 13.6 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{20}H_{28}O_5$ [M$^+$] 348.1937, found 348.1905.



Bicyclo[4.3.0]decenone (3.103g) (Patrick Leveque master work)

Bicyclo[4,3,0]alkenone (**3.103g**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

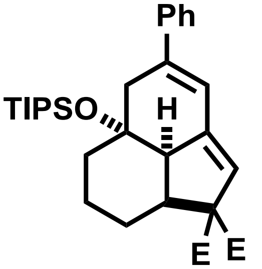
IR (neat, cm-1) ν max 2980, 2869, 1735, 1447, 1243; **^{1}H NMR (300MHz, CDCl$_3$)** δ = 7.37 - 7.15 (m, 5 H), 6.94 (dd, *J* = 11.3, 15.4 Hz, 1 H), 6.39 (d, *J* = 15.5 Hz, 1 H), 6.27 (d, *J* = 11.2 Hz, 1 H), 4.32 - 4.09 (m, 4 H), 3.87 - 3.77 (m, 1 H), 3.51 (d, *J* = 18.0 Hz, 1 H), 3.28 (td, *J* = 6.3, 12.3 Hz, 1 H), 2.96 (d, *J* = 18.1 Hz, 1 H), 2.40 - 2.31 (m, 2 H), 2.04 (td, *J* = 4.2, 13.5 Hz, 1 H), 1.78 - 1.58 (m, 2 H), 1.49 - 1.36 (m, 1 H), 1.25 (td, *J* = 7.1, 10.0 Hz, 6 H); **^{13}C NMR (75MHz, CDCl$_3$)** δ = 211.3 (C$_{quat}$), 170.5 (C$_{quat}$), 169.0 (C$_{quat}$), 137.3 (C$_{quat}$), 136. (C$_{quat}$), 133.0 (CHx2), 128.6 (CH), 127.5 (CH), 127.2 (CH), 126.4 (CHx2), 124.2 (CH), 62.7 (C$_{quat}$), 61.8 (CH$_2$), 61.7 (CH$_2$), 56.5 (CH), 48.3 (CH), 39.6 (CH$_2$), 39.5 (CH$_2$), 24.6 (CH$_2$), 24.3 (CH$_2$), 14.1 (CH$_3$), 14.0 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{24}H_{28}O_5$ [M$^+$] 396.1937, found 396.1940.



Diene (3.102g) (Patrick Leveque master work

Diene (3.102g) was prepared according to the general procedure G gold-catalyzed carbocyclization with **$\mathbf{Me_4tBuXPhos}$**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

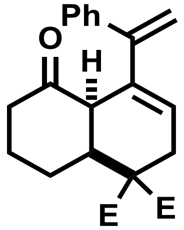
IR (neat, cm-1) ν max 2939, 1733, 1711, 1450, 1235, 1178, 694; **^{1}H NMR (300MHz, CDCl$_3$)** δ = 7.37 - 7.15 (m, 5 H), 6.56 (s, 2 H), 6.02 (td, *J* = 2.7, 5.5 Hz, 1 H), 4.26 - 4.15 (m, 4 H), 3.63 (br. s., 1 H), 3.06 - 2.94 (m, 2 H), 2.83 (td, *J* = 3.3, 20.0 Hz, 1 H), 2.39 - 2.20 (m, 2 H), 2.10 - 2.01 (m, 1 H), 1.77 - 1.53 (m, 3 H), 1.25 (dt, *J* = 5.5, 7.1 Hz, 6 H); **^{13}C NMR (101MHz ,CDCl$_3$)** δ = 213.0 (C$_{quat}$), 169.8 (C$_{quat}$), 169.4 (C$_{quat}$), 137.2 (C$_{quat}$), 131.4 (C$_{quat}$), 128.9 (CH), 128.7 (CH), 128.5 (CHx2), 127.5 (CH), 126.4 (CHx2), 125.8 (CH), 61.9 (CH$_2$), 61.8 (CH$_2$), 56.3 (C), 52.3 (CH), 41.1 (CH), 39.6 (CH$_2$), 27.5(CH$_2$), 26.1 (CH$_2$), 23.6 (CH$_2$), 14.0 (CH$_3$), 14.0 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{24}H_{28}O_5$ [M+] 396.1936, found 396.1942.



Tricycle (3.101h) (Patrick Leveque master work)

Tricycle (**3.101h**) was prepared according to the general procedure G gold-catalyzed carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

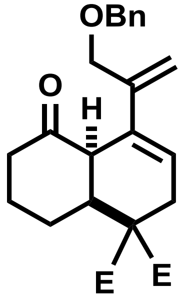
IR (neat, cm-1) ν max 2942, 2865, 1732, 1241, 1217, 1060, 883, 761, 674; **^{1}H NMR (300MHz, CDCl$_3$)** δ = 7.46 - 7.21 (m, 5 H), 6.64 (d, *J* = 2.8 Hz, 1 H), 5.76 (d, *J* = 2.8 Hz, 1 H), 4.30 - 4.06 (m, 4 H), 3.37 - 3.25 (m, 2 H), 2.87 (dd, *J* = 2.7, 16.9 Hz, 1 H), 2.65 (d, *J* = 16.3 Hz, 1 H), 1.95 - 1.73 (m, 1 H), 1.25 (td, *J* = 7.1, 18.4 Hz, 6 H), 1.13 (s, 18 H), 1.52 - 0.84 (m, 8 H); **^{13}C NMR (75MHz, CDCl$_3$) δ** = 170.2 (C$_{quat}$), 169.0 (C$_{quat}$), 145.1 (C$_{quat}$), 141.0 (C$_{quat}$), 140.7 (C$_{quat}$), 128.5 (CHx2), 127.8 (CH), 125.4 (CHx2), 122.3 (CH), 119.2 (CH), 72.3 (C_{quat}), 69.6 (C_{quat}), 61.2 (CH_2), 61.1 (CH_2), 51.7 (CH), 43.6 (CH_2), 42.6 (CH), 34.1(CH_2), 23.1 (CH_2), 19.1 (CH_2), 18.5 (CHx3), 14.2 (CH_3), 14.0 (CH_3), 13.7 (CH_3x6); **HRMS (EI)** m/z calcd for $C_{33}H_{48}O_5Si$ [M^+] 552.3271, found 552.3275.



Diene (3.102h) (Patrick Leveque master work)

Diene (**3.102h**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **Me_4tBuXPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

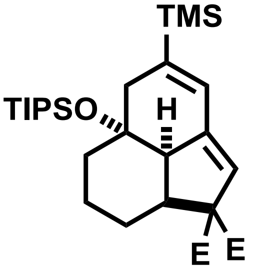
IR (neat, cm-1) ν max 2980, 2940, 1733, 1717, 1180, 780, 701; **^{1}H NMR (300MHz, $CDCl_3$)** δ = 7.33 - 7.20 (m, 5 H), 5.85 (td, *J* = 2.6, 5.4 Hz, 1 H), 5.19 (d, *J* = 1.2 Hz, 1 H), 5.09 (d, *J* = 1.2 Hz, 1 H), 4.27 - 4.15 (m, 4 H), 3.52 (br. s., 1 H), 3.04 - 2.90 (m, 2 H), 2.75 (ddd, *J* = 2.5, 4.1, 19.3 Hz, 1 H), 2.42 - 2.29 (m, 1 H), 2.26 - 2.17 (d, *J* = 12.6 Hz, 1 H), 2.13 - 2.00 (m, 1 H), 1.79 - 1.59 (m, 3 H), 1.25 (dt, *J* = 1.5, 7.1 Hz, 6 H); **^{13}C NMR (75MHz ,$CDCl_3$)** δ = 210.6 (C_{quat}), 169.8 (C_{quat}), 169.6 (C_{quat}), 149.2 (C_{quat}), 140.1 (C_{quat}), 134.2 (C_{quat}), 128.2 (CHx2), 127.8 (CH), 127.4 (CHx2), 126.6 (CH), 114.6 (CH_2), 61.9 (CH_2), 61.7 (CH_2), 56.2 (C), 52.4 (CH), 40.6 (CH), 39.7 (CH_2), 27.2 (CH_2), 25.6 (CH_2), 23.6 (CH_2), 14.0 (CH_3), 14.0 (CH_3); **HRMS (EI)** m/z calcd for $C_{24}H_{28}O_5$ [M^+] 396.1937, found 396.1918.



Diene (3.102i) (Patrick Leveque master work)

Diene (**3.102i**) was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **Me_4tBuXPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm-1) ν max 2979, 2942, 2866, 1732, 1366, 1217, 1180, 1094, 913, 738, 699; **^{1}H NMR (400MHz ,CDCl$_3$)** δ = 7.37 - 7.23 (m, 5 H), 5.89 (td, *J* = 2.6, 5.5 Hz, 1 H), 5.11 (d, *J* = 0.9 Hz, 1 H), 5.06 (s, 1 H), 4.46 (dd, *J* = 11.9, 27.3 Hz, 2 H), 4.31 - 4.06 (m, 5 H), 3.99 (d, *J* = 12.7 Hz, 1 H), 3.66 (s, 1 H), 3.02 - 2.84 (m, 2 H), 2.75 (ddd, *J* = 2.8, 3.9, 19.4 Hz, 1 H), 2.42 - 2.23 (m, 1 H), 2.18 (d, *J* = 12.6 Hz, 1 H), 2.06 - 1.96 (m, 1 H), 1.71 - 1.53 (m, 3 H), 1.21 (td, *J* = 7.1, 19.0 Hz, 6 H); **^{13}C NMR (101MHz , CDCl$_3$)** δ = 212.3 (C$_{quat}$), 169.9 (C$_{quat}$), 169.4 (C$_{quat}$), 144.6 (C$_{quat}$), 138.3 (C$_{quat}$), 132.7 (C$_{quat}$), 128.3 (CHx2), 127.7 (CHx2), 127.5 (CH), 123.7 (CH), 115.4 (CH$_2$), 72.1 (CH$_2$), 71.7 (CH$_2$), 61.8 (CH$_2$), 61.8 (CH$_2$), 56.1 (C), 52.4 (CH), 40.7 (CH), 39.5 (CH$_2$), 27.1 (CH$_2$), 25.9 (CH$_2$), 23.5 (CH$_2$), 14.0 (CH$_3$), 14.0 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{26}H_{32}O_6$ [M$^+$] 440.2199, found 440.2204.

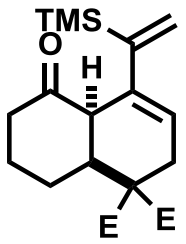


Tricycle (Patrick Leveque master work)

Tricycle was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **JohnPhos**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

Compound aromatizes readily in CDCl$_3$. Use of deactivated silica (washed with 1% Et$_3$N in hexanes) was necessary for flash chromatography purification.

IR (neat, cm-1) ν max 2943, 2866, 1733, 1464, 1242, 1221, 1118, 1059, 835, 679; **^{1}H NMR (300MHz, C$_6$D$_6$)** δ = 6.48 (d, *J* = 2.8 Hz, 1 H), 6.06 (d, *J* = 2.8 Hz, 1 H), 4.20 - 3.68 (m, 5 H), 3.65 - 3.59 (m, 1 H), 2.59 (dd, *J* = 3.3, 16.6 Hz, 1 H), 2.41 (d, *J* = 16.6 Hz, 1 H), 2.15 - 1.95 (m, 1 H), 1.78 - 1.60 (m, 1 H), 1.55 - 1.31 (m, 4 H), 1.27 - 1.07 (m, 21 H), 0.93 (td, *J* = 7.1, 16.5 Hz, 6 H), 0.07 (s, 9 H); **^{13}C NMR (75MHz, C$_6$D$_6$)** δ = 169.4 (C$_{quat}$), 168.6 (C$_{quat}$), 144.9 (C$_{quat}$), 144.9 (C$_{quat}$), 129.6 (CH), 123.0 (CH), 72.4 (C$_{quat}$), 69.4 (C$_{quat}$), 60.8 (CH$_2$), 60.6 (CH$_2$), 52.1 (CH), 43.3 (CH$_2$), 43.3 (CH), 34.0 (CH$_2$), 23.3 (CH$_2$), 19.3 (CH$_2$), 18.5 (CHx3), 13.8 (CH$_3$), 13.7 (CH$_3$x6), 13.7 (CH$_3$), -2.9 (CH$_3$x3); **HRMS (EI)** m/z calcd for $C_{27}H_{45}O_5Si_2$ [(M-$_i$Pr)$^+$] 505.2806, found 505.2809.

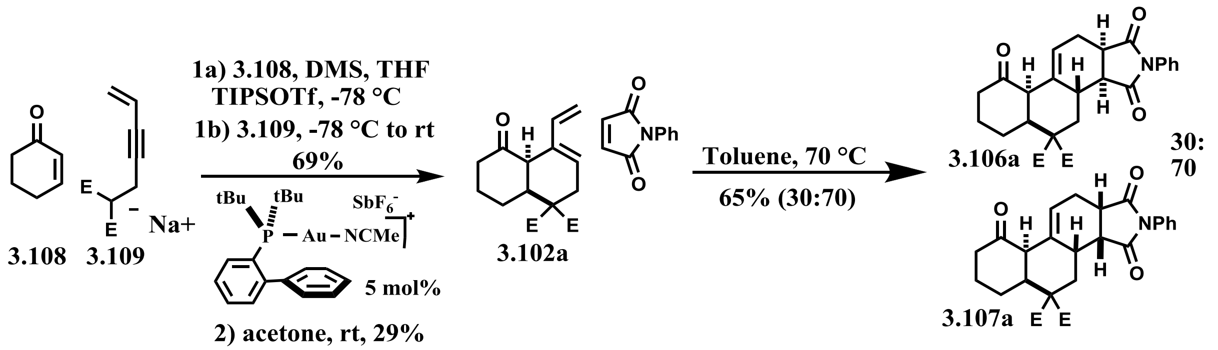


Diene (2.11c) (Patrick Leveque master work)

Diene was prepared according to the **general procedure G** gold-catalyzed carbocyclization with **Me_4tBuXPhos**AuNCMeSbF_6 as catalyst and isolated as a clear oil.

IR (neat, cm-1) ν max 2954, 1733, 1714, 1249, 1179, 841, 760; **^{1}H NMR (300MHz, $CDCl_3$)** δ = 5.52 (d, J = 2.7 Hz, 1 H), 5.47 (td, J = 2.5, 5.4 Hz, 1 H), 5.31 (d, J = 2.7 Hz, 1 H), 4.31 - 4.08 (m, 4 H), 3.59 (br. s., 1 H), 3.01 - 2.81 (m, 2 H), 2.71 (ddd, J = 2.5, 3.9, 19.0 Hz, 1 H), 2.35 - 1.92 (m, 3 H), 1.71 - 1.53 (m, 3 H), 1.24 (t, J = 7.1 Hz, 6 H), 0.08 (s, 9 H); **^{13}C NMR (75MHz, $CDCl_3$)** δ = 211.1 (C_{quat}), 169.9 (C_{quat}), 169.6 (C_{quat}), 152.9 (C_{quat}), 137.3 (C_{quat}), 126.7 (CH_2), 120.7 (CH), 61.7 (CH_2), 61.6 (CH_2), 56.1 (C_{quat}), 53.2 (CH), 40.4 (CH), 40.3 (CH_2), 26.8 (CH_2), 25.5 (CH_2), 23.6 (CH_2), 14.0 (CH_3), 14.0 (CH_3), -0.8 (CH_3x3); **HRMS (EI)** m/z calcd for $C_{21}H_{32}O_5Si$ [M^+] 392.2019, found 392.2023.

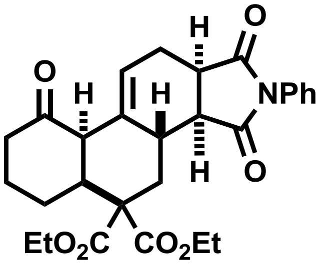
Trace: ^{1}H NMR (500MHz ,$CDCl_3$) δ = 6.00 (s, 1 H), 5.49 (d, J = 2.8 Hz, 1 H), 4.30 - 4.04 (m, 4 H), 3.27 - 3.22 (m, 1 H), 3.16 - 3.12 (m, 1 H), 2.49 (d, J = 16.9 Hz, 1 H), 2.04 (d, J = 16.9 Hz, 1 H), 1.79 (s, 3 H), 1.29 - 1.18 (m, 6 H), 1.12 - 1.07 (m, 18 H), 1.83 - 0.68 (m, 9 H); **^{13}C NMR (126MHz, $CDCl_3$)** δ = 170.4 (C_{quat}), 169.3 (C_{quat}), 145.0 (C_{quat}), 140.9 (C_{quat}), 118.6 (CH), 118.2 (CH), 72.2 (C_{quat}), 69.4 (C_{quat}), 61.0 (CH_2), 60.9 (CH_2), 51.4 (CH), 46.5 (CH_2), 42.4 (CH), 34.4 (CH_2), 23.9 (CH_3), 23.2 (CH_2), 19.1 (CH_2), 18.5 (CHx3), 14.1 (CH_3), 14.1 (CH_3), 13.7 (CH_3x6).



Scheme 7.09 *Three steps synthesis of polyclic framework related to steroid from cyclohexenone*

General Procedure H- Diels-Alder reaction

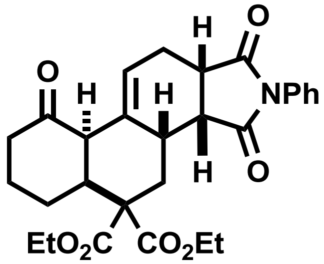
N-phenylmaleimide (16.8 mg, 0.0963 mmol) was canulated with toluene (0.24 mL) to a solution of the diene **2.8c** (19.3 mg, 0.0602 mmol) in toluene (0.40 mL) at room temperature in a sealed tube. The reaction mixture was then stirred for 3 day at 70°C. Once the reaction was completed, the solvent was evaporated and the residue was purified by flash column chromatography (40% EtOAc : Hexane) to yield 5.8 mg of **2.14a** and 13.4 mg of **2.14b** as colorless oils in a total 65% yield.



Diterpene (3.106a) (Patrick Leveque master work)

Diterpene (**3.106a**) was prepared according to the **general procedure H** Diels-Alder reaction and isolated as a white solid.

IR (neat, cm^{-1})) ν max 1710; **^{1}H NMR (500MHz, CDCl$_3$)** δ = 7.53 - 7.40 (m, 2 H), 7.39 - 7.34 (m, 1 H), 7.17 - 7.13 (m, 2 H), 5.45 (qd, *J* = 2.8, 7.2 Hz, 1 H), 4.33 - 4.18 (m, *J* = 7.1, 7.1, 7.1, 10.6, 10.6 Hz, 2 H), 4.12 (qt, *J* = 7.1, 10.6 Hz, 2 H), 3.34 - 3.26 (m, 2 H), 3.19 (ddd, *J* = 3.4, 4.8, 13.0 Hz, 1 H), 3.09 - 2.98 (m, 1 H), 2.83 (dd, *J* = 7.1, 15.6 Hz, 1 H), 2.64 (dd, *J* = 4.5, 14.9 Hz, 1 H), 2.57 - 2.43 (m, 2 H), 2.38 - 2.25 (m, 2 H), 1.98 (ddd, *J* = 2.6, 7.1, 13.4 Hz, 1 H), 1.72 - 1.59 (m, *J* = 4.5, 4.5, 4.5, 8.7, 13.1 Hz, 2 H), 1.59 - 1.50 (m, 1 H), 1.36 (dq, *J* = 3.7, 12.8 Hz, 1 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H); **^{13}C NMR (126MHz, CDCl$_3$)** δ = 209.6 (C$_{quat}$), 178.4 (C$_{quat}$), 176.5 (C$_{quat}$), 171.4 (C$_{quat}$), 171.2 (C$_{quat}$), 138.6 (C$_{quat}$), 131.6 (C$_{quat}$), 129.1 (2xCH), 128.7 (CH), 126.6 (2xCH), 122.0 (CH), 61.9 (CH$_2$), 61.2 (CH$_2$), 55.3 (C$_{quat}$), 53.1 (CH), 43.1 (CH), 39.6 (CH), 39.0 (CH), 37.8 (CH$_2$), 32.0 (CH), 29.6 (CH$_2$), 24.8 (CH$_2$), 24.7 (CH$_2$), 24.3 (CH$_2$), 14.0 (CH$_3$), 13.9 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{28}H_{31}NO_7$ [(M)$^+$] 493.2101, found 493.2087.



Diterpene (3.107a) (Patrick Leveque master work)

Diterpene (**3.107a**) was prepared according to the **general procedure H** Diels-Alder reaction and isolated as a white solid.

IR (neat, cm^{-1})) ν max 1713; **^{1}H NMR (500MHz, $CDCl_3$)** δ 7.50 - 7.43 (m, 2 H), 7.41 - 7.36 (m, 1 H), 7.35 - 7.31 (m, 2 H), 5.54 (qd, *J* = 2.7, 6.4 Hz, 1 H), 4.28 - 4.09 (m, 4 H), 3.35 - 3.30 (m, 1 H), 3.13 - 3.02 (m, 3 H), 2.79 - 2.64 (m, 2 H), 2.53 (ddd, *J* = 6.7, 13.0, 15.4 Hz, 1 H), 2.34 - 2.21 (m, 2 H), 2.03 - 1.93 (m, 1 H), 1.79 - 1.57 (m, 4 H), 1.47 (dq, *J* = 3.7, 13.0 Hz, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H); **^{13}C NMR (126MHz, $CDCl_3$)** δ 209.9 (C_{quat}), 178.0 (C_{quat}), 177.4 (C_{quat}), 171.5 (C_{quat}), 170.5 (C_{quat}), 135.9 (C_{quat}), 131.9 (C_{quat}), 129.2 (2xCH), 128.6 (CH), 126.5 (2xCH), 123.4 (CH), 62.0 (CH_2), 61.5 (CH_2), 55.7 (C_{quat}), 53.3 (CH), 45.5 (CH), 39.5 (CH), 38.8 (CH), 37.8 (CH_2), 33.7 (CH_2), 31.8 (CH), 25.0 (CH_2), 24.6 (CH_2), 23.7 (CH_2), 14.2 (CH_3), 14.2 (CH_3); **HRMS (EI)** m/z calcd for $C_{28}H_{31}NO_7$ [$(M)^+$] 493.2101, found 493.2021.

References

(1) Maeyama, K., Kusama, H., Iwasawa, N. *J. Am. Chem. Soc.*, **1998**, 120, 1928.

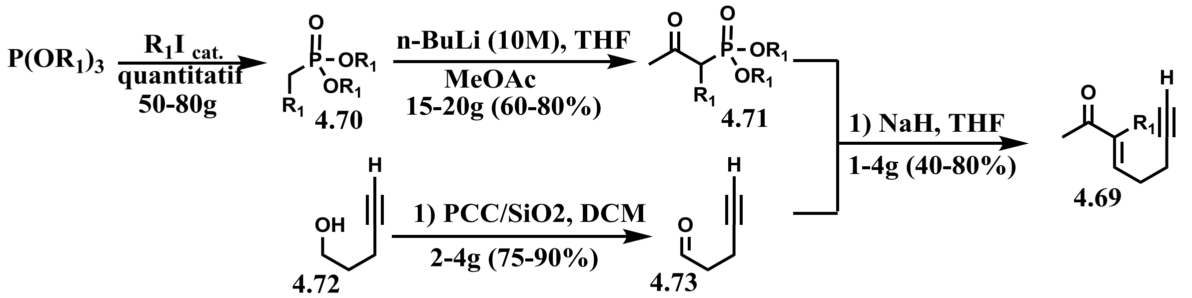
(2) Sunngak, K., Park, J. H., Kim, Y. G., Lee, J. M., *J. Chem. Soc., Chem. Commun.,* **1993,** 15, 1188-1189.

(3) Maeyama, K., Kusama, H., Iwasawa, N. *Org. Lett.*, **2001**, 3, 3871.

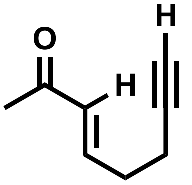
(4) Bull, J. A., Mousseau, J. J., Charette, A. B., *Org. Synth.* **2010**, *87*, 170-177.

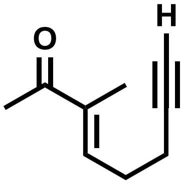
(5)Kutsumura, N., Niwa, K., Saito, T., *Org. Lett.*, **2010**, *15*, 3316

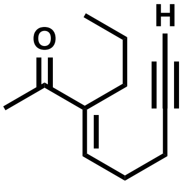
7.8 Detailed Experimental: Synthesis of the linear precursor, an diene silyl enol ether- enyne



Scheme 7.10 *Known convergent synthesis of enone*







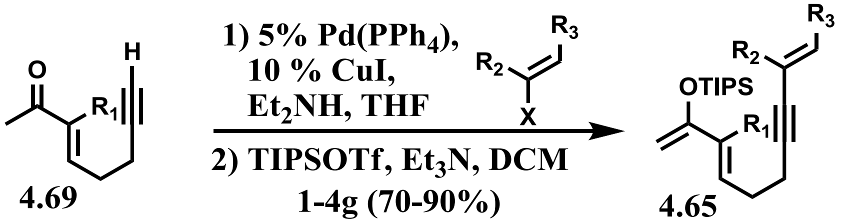
Synthesis and spectral data is in accordance with reported data and full characterization is available through the literature[1]

General Procedure F: Sonogashira reaction

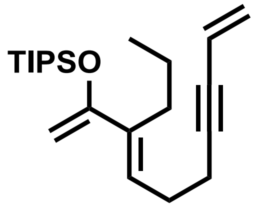
A flame-dried flask equipped with a magnetic stir bar was charged with $Pd(PPh_3)_4$ (0.05 mmol) followed by CuI (0.1 mmol). Benzene or THF (10.0 mL) was then added and the solution was degassed with argon for 15 minutes. During the degassing, the terminal alkyne (1.0 mmol) was added followed by vinyl halide (1.5-3.0 mmol). Once the degassing was completed, diethyl amine (5.0 mmol) was added to the solution and the mixture was stirred overnight. Silica was added directly to the mixture and the solvent was evaporated off under reduced pressure. The residue was then purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (90:10 to 80:20)) to give the desired compound as a clear yellow oil (60-100% yield).

General Procedure I: Silyl enol ether formation

Enone (2.00 mmol) was dissolved in DCM (10 mL) and Et_3N (4.00 mmol) was added. The mixture was cooled to 0 °C and TBSOTf (3.00 mmol). The mixture was stirred for 1 h at 0 °C and quenched with saturated $NaHCO_3$. The aqueous layer was extracted 2 times with DCM. The organics layers was combined, dried over $MgSO_4$ and filtered. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (98:2 to 95:5)) to give the enol ether as a clear oil.



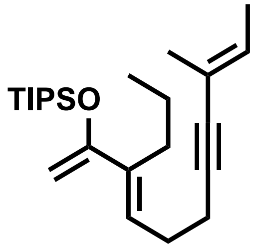
Scheme 7.11 *Synthesis of diene silyl enol ether-enyne*



Triisopropyl(3-propyldeca-1,3,9-trien-7-yn-2-yl]oxy})silane (4.65g)

Diene-enyne (**4.65g**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

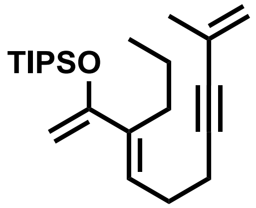
IR (neat, cm^{-1}) ν max 2952, 2865, 1581, 1289, 1034, 681; **^{1}H-NMR (400 MHz; *CDCl$_3$*):** δ δ 6.20-6.10 (m, 1H), 5.74 (tdd, J = 17.8 Hz, 11.1 Hz, 1.8Hz 1H), 5.53 (dd, J = 17.8 Hz, 1.8 Hz, 1H), 5.36 (dd, J = 11.1 Hz, 2.3 Hz, 1H), 4.40 (d, J =1.1 Hz, 1H), 4.27 (s, 1H), 2.41-2.34 (m, 1H), 2.39 (s, 3H), 2.20 (dd, *J* = 9.0, 6.8 Hz, 2H), 1.52-1.42 (m, 2H), 1.32-1.21 (m, 3H), 1.11 (d, J = 7.1 Hz, 18H), 0.94 (t, J = 7.4 Hz, 3H). **^{13}C NMR (101 MHz; *CDCl$_3$*):** δ 156.5, 136.8, 126.49, 125.3, 117.6, 90.4, 90.3, 79.6, 29.7, 27.6, 22.6, 19.4, 18.2, 14.5, 12.9: **HRMS (EI**) m/z calcd for $C_{22}H_{38}OSi$ [$(M-C_3H_7)^+$] = 303.2144, found mass = 303.2134.



Triisopropyl{[(9-methyl-3-propylundeca-1,3,9-trien-7-yn-2-yl)oxy]}silane (4.65h)

Diene-enyne (**4.65h**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

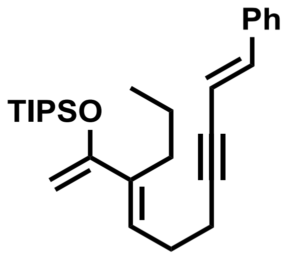
IR (neat, cm^{-1}) ν max 2952, 2879, 1588, 1465, 1289, 1022, 674; **^{1}H-NMR (400 MHz; *CDCl$_3$*):** δ 6.09 (t, J = 7.5 Hz, 1H), 5.82 (qd, *J* = 7.0, 1.5 Hz, 1H), 4.37 (d, J = 0.9 Hz, 1H), 4.24 (s, 1H), 2.35-2.22 (m, 4H), 1.78 (s, 3H), 1.76 (quin, *J* = 1.2 Hz, 3H), 1.67-1.58 (m, 7H, 1.28-1.21 (m, 3H), 1.09 (d, J = 7.1 Hz, 18H), 0.93 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (101 MHz; *CDCl$_3$*):** δ 156.9, 137.0, 130.9, 126.7, 118.9, 90.4, 85.8, 83.8, 29.8, 28.0, 22.9, 19.5, 18.21, 17.9, 17.3, 14.2, 12.4: **HRMS (EI**) m/z calcd for $C_{24}H_{42}OSi$ [$(M-C_3H_7)^+$] = 331.2457, found mass = 331.2443.



Triisopropyl{[(9-methyl-3-propyldeca-1,3,9-trien-7-yn-2-yl)oxy]}silane (4.65i)

Diene-enyne (**4.65i**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

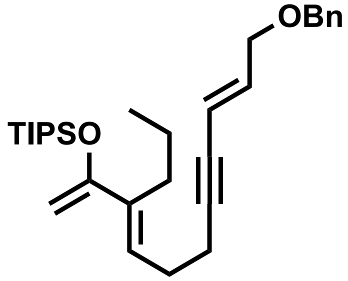
IR (neat, cm^{-1}) ν max 2949, 2867, 1593, 1455, 1303, 1017, 881; **^{1}H-NMR (400 MHz; *CDCl$_3$*):** δ 6.09 (t, *J* = 7.1 Hz, 1H), 5.19 (m, 1H), 5.13 (dq, J = 1.7 Hz, 1H), 4.41 (s, 1H). 4.27 (s, 1H), 2.38-2.35 (m, 1H), 2.37 (s, 3H), 2.21-2.17 (m, 2H), 1.85 (t, *J* = 1.3 Hz, 3H), 1.50-1.36 (m, 2H), 1.27-1.21 (m, 3H), 1.10 (d, J = 7.1 Hz, 18H), 0.93 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (101 MHz; *CDCl$_3$*):** δ 156.7, 137.1, 127.4, 126.7, 120.6, 90.5, 88.9, 82.2, 77.4, 29.8, 27.9, 22.7, 19.8, 18.2, 14.5, 12.9. **HRMS (EI**) m/z calcd for $C_{23}H_{40}OSi$ [$(M-C_3H_7)^+$] =317.2301, found mass = 317.2281.



Triisopropyl{[(3-propyl-10-phenyldeca-1,3,9-trien-7-yn-2-yl)oxy]}silane (4.65j)

Diene-enyne (**4.65j**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

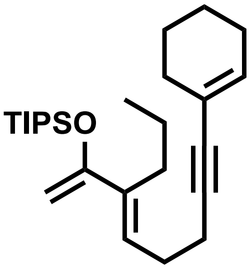
IR (neat, cm^{-1}) ν max 3013, 2971, 2878, 1589, 1463, 1278, 1022, 881, 673; **^{1}H-NMR (400 MHz; *CDCl$_3$*):** δ 7.37-7.28 (m, 5H), 6.86 (d, *J* = 16.2 Hz, 1H), 6.18-6.12 (m, 1H), 6.11 (dt, J = 16.4 Hz, 2.2 Hz, 1H), 4.40 (s, 1H), 4.26 (s, 1H), 2.46-2.44 (m, 2H), 2.21-2.16 (m, 2H), 2.25-2.19 (m, 2H), 1.52-1.43 (m, 2H), 1.27-1.19 (m, 3H), 1.09 (d, J = 7.1 Hz, 18H), 0.94 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (101 MHz; *CDCl$_3$*):** δ 156.7, 140.3, 137.1, 136.7, 128.8, 128.4, 126.7, 126.2, 109.0, 92.5, 90.5, 80.2, 29.9, 27.9, 22.8, 20.2, 18.2, 12.9, 14.4: **HRMS (EI**) m/z calcd for $C_{28}H_{42}OSi$ =422.3005, found mass = 422.3013.



Triisopropyl{[11-(benzyloxy)-3-propylundeca-1,3,9-trien-7-yn-2-yl]oxy}silane (4.65k)

Diene-enyne (**4.65k**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

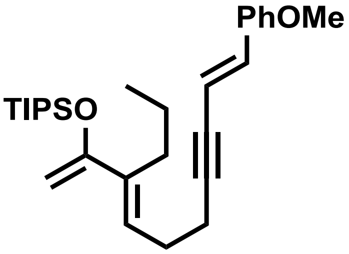
IR (neat, cm^{-1}) ν max 2955, 2876, 1467, 1286, 1259, 1019, 880; **^{1}H-NMR (400 MHz; *CDCl$_3$*):** δ 7.37-7.27 (m, 5H), 6.14-6.07 (m, 2H), 5.72 (dt, *J* = 15.9, 1.7 Hz, 1H), 4.51 (s, 2H), 4.41 (d, J= 1.1 Hz, 1H), 4.28 (d, J= 1.1 Hz, 1H), 4.04 (dd, *J* = 5.7 Hz, 1.7 Hz, 2H), 2.40-2.32 (m, 4H), 2.20-2.16 (m, 2H), 1.50-1.39 (m, 2H), 1.27-1.19 (m, 3H), 1.09 (d, J = 7.1 Hz, 18H), 0.92 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (101 MHz; *CDCl$_3$*):** δ 156.6, 138.2, 138.1, 137.9, 137.0, 128.4, 127.6, 126.5, 112.5, 90.8, 90.6, 78.8, 72.1, 69.9, 29.9, 27.9, 22.5, 19.7, 18.1, 14.3, 12.9: **HRMS (EI**) m/z calcd for $C_{30}H_{46}O_2Si$ [$(M-C_3H_7)^+$] = 423.2719, found mass = 423.2689.



Triisopropyl [(8-(cyclohex-1-en-1-yl)-3-propylocta-1,3-dien-7-yn-2-yl)oxy]silane (4.65l)

Diene-enyne (**4.65l**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

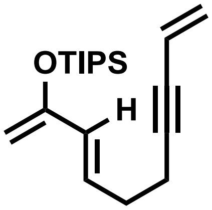
IR (neat, cm^{-1}) ν max 2938, 2866, 14667, 1271, 1266, 1025, 879 ; **^{1}H-NMR (400 MHz; *CDCl$_3$*):** δ 6.11 (dt, *J* = 15.2, 4.7 Hz, 1H), 5.98 (dt, *J* = 3.8, 1.9 Hz, 1H), 4.41 (s, 1H), 4.27 (s,1H), 2.35-2.33 (m, 4H), 2.20-2.16 (m, 2H), 2.11-2.02 (m, 4H), 1.64-1.53 (m, 4H), 1.46 (dq, J = 7.5 Hz, 15.3 Hz, 2H), 1.27-1.10 (m, 3H), 1.10 (d, J = 7.1 Hz, 18H), 0.91 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (101 MHz; *CDCl$_3$*):** δ 156.7, 136.8, 133.3, 126.9, 121.1, 90.4, 86.8, 82.6, 29.8, 29.6, 28.1, 25.7, 22.8, 22.5, 21.7, 19.8, 18.2, 14.4, 12.9: **HRMS (EI**) m/z calcd for $C_{26}H_{44}OSi$ =400.3161, found mass = 400.3155



Triisopropyl({[10-(4-methoxyphenyl)-3-propyldeca-1,3,9-trien-7-yn-2-yl]oxy})silane (4.65m)

Diene-enyne (**4.65m**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

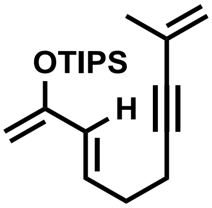
IR (neat, cm^{-1}) ν max 2948, 2862, 1448, 1288, 1036, 878; **IR (neat, cm^{-1})** ν max **^{1}H-NMR (400 MHz; *CDCl$_3$*):** δ 7.33-7.29(m, 2H), 6.88-6.84 (m, 2H), 6.82 (d, *J* = 16.2 Hz, 1H), 6.18 (t, J = 6.9 Hz, 1H)), 6.01 (dt, J = 16.2 Hz, 2Hz, 1H), 4.45 (d, *J* = 1.0 Hz, 1H), 4.30 (d, J = 1.0 Hz, 1H), 3.81 (s, 3H), 2.48-2.39 (m, 4H), 2.28 (t, J = 7.7 Hz, 2H), 1.49 (dt, J = 15.3 Hz, 7.5 Hz, 2H), 1.32-1.21 (m, 3H), 1.12 (d, J = 7.1 Hz, 18H), 0.96 (t, J = 7.4 Hz, 3H). **^{13}C NMR (101 MHz; *CDCl$_3$*):** δ 159.6, 156.6, 139.7, 136.9, 129.6, 127.4, 126.7, 114.2, 106.5, 91.5, 90.5, 80.4, 90.5, 80.4, 55.3, 29.8, 27.9, 22.8, 20.1, 18.2, 14.5, 12.9: **HRMS (EI**) m/z calcd for $C_{29}H_{44}O_2Si$ = 452.3111, found mass = 452.3156.



Triisopropyl(deca-1,3,9-trien-7-yn-2-yl]oxy})silane (4.65n)

Diene-enyne (**4.65n**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2948, 2869, 1579, 1297, 1022, 678; **^{1}H-NMR (400 MHz; *CDCl$_3$*):** δ 6.16-6.08 (m, 1H), 5.93 (d, *J* = 15.2 Hz, 1H), 5.74 (tdd, J = 17.5 Hz, 11.0 Hz, 2.0 Hz, 1H), 5.51 (dd, J = 17.6 Hz, 2.3 Hz, 1H), 5.31 (dd, J = 10.9 Hz, 2.3 Hz, 1H), 4.24 (s, 1H), 4.18 (s, 1H), 2.37 (m, 4H), 1.29-1.17 (m, 3H), 1.12 (d, J = 7.1 Hz, 18H), **^{13}C NMR (101 MHz; *CDCl$_3$*):** δ 155.2, 129.4, 129.1, 125.5, 117.6, 93.7, 90.2, 79.9, 31.3, 19.6, 18.1, 12.9: **HRMS (EI**) m/z calcd for $C_{19}H_{32}OSi$ = 304.2222, found mass = 304.2243

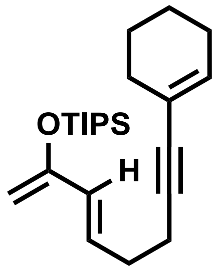


Triisopropyl{[(9-methyldeca-1,3,9-trien-7-yn-2-yl)oxy]}silane (4.65o)

Diene-enyne (**4.65o**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2954,, 2867, 1576, 1288, 1023, 738; **^{1}H-NMR (400 MHz; *CDCl$_3$*):** δ 6.16-6.08 (m,1H), 5.91 (d, *J* = 15.2 Hz, 1H), 5.19 (s, 1H), 5.13 (s, 1H), 4.24 (s, 1H), 4.19 (s, 1H), 2.40-2.31 (m, 4H), 1.84 (s, 3H), 11.28-1.19 (m, 3H), 1.11 (d, J = 7.1 Hz, 18H). **^{13}C NMR (101 MHz; *CDCl$_3$*):** δ

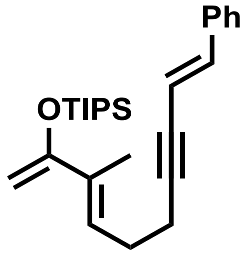
155.3, 129.5, 129.2 , 127.4, 120.7, 93.9, 88.7, 82.5, 31,6, 23.9, 19.6, 18.1, 12.9 : **HRMS (EI)** m/z calcd for $C_{20}H_{34}O_1Si$ [$(M-C_3H_7)^+$] =275.1831, found mass = 275.1830.



Triisopropyl[(8-(cyclohex-1-en-1-yl)octa-1,3-dien-7-yn-2-yl)oxy]silane (4.65p)

Diene-enyne (**4.65p**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2933, 2858, 1456, 1275, 1258, 1034, 883; **^{1}H-NMR (400 MHz; *CDCl₃*):** δ 6.13 (dt, *J* = 15.2, 6.7 Hz, 1H), 6.01 (dt, *J* = 3.8, 1.9 Hz, 1H), 5.92 (dt, *J* = 15.2, 1.2 Hz, 1H), 4.25 (s, 1H), 4.20 (s,1H), 2.40-2.29 (m, 4H), 2.10-2.04 (m, 4H), 1.64-1.53 (m, 4H), 1.27-1.20 (m, 3H), 1.10 (d, J = 7.1 Hz, 18H). **^{13}C NMR (101 MHz; *CDCl₃*):** δ 155.3 (C_{quat}), 133.5 (CH), 129.9 (CH), 129.1 (CH), 121.1 (C_{quat}), 94.0 (CH_2), 86.6 (C_{quat}), 82.9 (C_{quat}), 32.0 (CH_2), 29.8 (CH_2), 25.8 (CH_2), 22.7 (CH_2), 21.6 (CH_2), 19.5 (CH_2), 18.2 (CH_3x6), 12.9 (CHx3). **HRMS (EI)** m/z calcd for $C_{23}H_{38}OSi$ = 358.2692, found mass = 358.2706



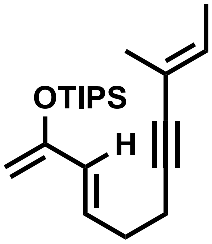
Triisopropyl{[(3-methyl-10-phenyldeca-1,3,9-trien-7-yn-2-yl)oxy]}silane (4.65s)

(Guillaume Revol post-Doctorate work)

Diene-enyne (**4.65s**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 3027.2, 2941.2, 2870.7, 1587.3, 1458.17, 1289.92, 1016.0, 879.1, 683.43. **^{1}H NMR (400 MHz, *CDCl₃*)** δ 7.38-7.29 (m, 4H), 7.29-7.23 (m, 1H), 6.86 (d, *J* = 16.23 Hz, 1H), 6.20 (t, *J* = 6.57 Hz, 1H), 6.14 (td, *J* = 16.25, 2.05 Hz, 1H), 4.41 (d, *J* = 1.01 Hz, 1H), 4.28 (s, 1H), 2.49-2.37

(m, 4H), 1.80 (d, *J* = 0.72 Hz, 3H), 1.34-1.17 (m, 3H), 1.12 (s, 9H), 1.11 (s, 9H). **^{13}C NMR (101 MHz, *CDCl₃*)** δ 157.42, 140.10, 136.60, 132.09, 128.65, 126.35, 126.05, 108.83, 92.35, 90.50, 80.02, 27.78, 19.89, 18.15, 18.06, 17.72, 13.45, 12.87. **HRMS (EI**) m/z calcd for $C_{26}H_{38}O_1Si$ = 394.2692, found mass = 394.2698.

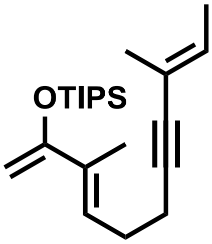


Triisopropyl{[(9-methylundeca-1,3,9-trien-7-yn-2-yl)oxy]}silane (4.65t)

(Guillaume Revol post-Doctorate work)

Diene-enyne (**4.65t**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

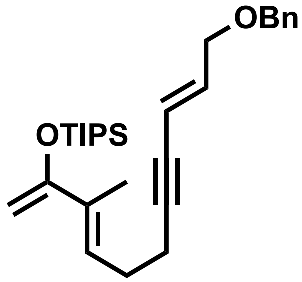
IR (neat, cm^{-1}) ν max 2945.1, 2866.8, 1466.0, 1250.8, 1016.0, 800.8, 675.6. **^{1}H NMR (400 MHz, *CDCl₃*)** δ 5.92 (td, *J* = 15.24, 1.16 Hz, 1H), 5.81 (dq, *J* = 7.02, 1.45 Hz, 1H), 4.24 (s, 1H), 4.19 (s, 1H), 2.42-2.27 (m, 4H), 1.78-1.70 (m, 3H), 1.68-1.61 (m, 3H), 1.30-1.17 (m, 3H), 1.10 (d, *J* = 6.98 Hz, 18H). **^{13}C NMR (101 MHz, *CDCl₃*)** δ 155.19, 130.94, 129.61, 128.94, 118.74, 93.57, 85.37, 84.11, 31.66, 19.47, 18.10, 17.15, 13.94, 12.83. **HRMS (EI**) m/z calcd for $C_{21}H_{36}O_1Si$ = 332.2535, found mass = 332.2552.



Triisopropyl[(3,9-dimethylundeca-1,3,9-trien-7-yn-2-yl)oxy]silane (4.65u) (Guillaume Revol post-Doctorate work)

Diene-enyne (**4.65u**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2945.0, 2870.7, 1595.1, 1462.1, 1297.8, 1019.9, 678.5. **^{1}H NMR (400 MHz, *$CDCl_3$*)** δ 6.14 (t, *J* = 6.61 Hz, 1H), 5.87-5.74 (m, 1H), 4.39 (d, *J* = 1.02 Hz, 1H), 4.26 (s, 1H), 2.38-2.34 (m, 4H), 1.77 (d, *J* = 0.91 Hz, 3H), 1.74 (m, 3H), 1.65 (dd, *J* = 7.03, 1.02 Hz, 3H), 1.30-1.18 (m, 3H), 1.10 (d, *J* = 7.06 Hz, 18H). **^{13}C NMR (101 MHz, *$CDCl_3$*)** δ 157.49, 131.92, 130.89, 126.60, 118.75, 90.37, 85.67, 83.77, 28.08, 19.51, 18.13, 17.13, 13.92, 13.43, 12.87. **HRMS (EI)** m/z calcd for $C_{22}H_{38}O_1Si$ = 346.2692, found mass = 346.2701.

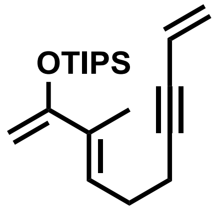


Triisopropyl{[11-(benzyloxy)-3-methylundeca-1,3,9-trien-7-yn-2-yl]oxy}silane (4.65v) (Guillaume Revol post-Doctorate work)

Diene-enyne (**4.65v**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2945.1, 2864.1, 1463.87, 1274.9, 1267.1, 1016.4, 881.41. **^{1}H NMR (400 MHz, *$CDCl_3$*)** δ 7.38-7.31 (m, 4H), 7.31-7.27 (m, 1H), 6.19-6.12 (m, 1H), 6.09 (t, *J* = 5.73 Hz, 1H), 5.72 (d, *J* = 15.89 Hz, 1H), 4.51 (s, 2H), 4.40 (s, 1H), 4.27 (s, 1H), 4.05 (dd, *J* = 5.65, 1.41 Hz, 1H), 2.43-2.34 (m, 4H), 1.78 (s, 3H), 1.32-1.16 (m, 3H), 1.10 (d, *J* = 7.13 Hz, 1H).

^{13}C NMR (101 MHz, *$CDCl_3$*) δ 157.34, 138.07, 137.91, 132.02, 128.37, 127.65, 127.62, 126.29, 112.50, 90.63, 90.46, 78.60, 72.03, 69.88, 27.69, 19.61, 18.11, 17.69, 12.81. **HRMS (EI)** m/z calcd for $C_{28}H_{42}O_2Si$ = 438.2954, found mass = 438.2961.

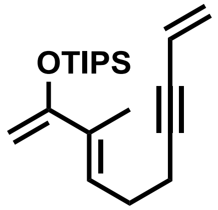


Triisopropyl(3-methyldeca-1,3,9-trien-7-yn-2-yl]oxy})silane (4.65w)

(Guillaume Revol post-Doctorate work)

Diene-enyne (**4.65w**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2945.1, 2866.8, 1587.3, 1297.8, 1020.0, 678.5. **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ 6.16 (t, *J* = 6.51 Hz, 1H), 5.75 (tdd, *J* = 17.52, 11.01, 1.95 Hz, 1H), 5.53 (dd, *J* = 17.51, 2.28 Hz, 1H), 5.37 (dd, *J* = 11.00, 2.29 Hz, 1H), 4.39 (d, *J* = 1.09 Hz, 1H), 4.27 (s, 1H), 2.41-2.35 (m, 4H), 1.77 (d, *J* = 0.81 Hz, 3H), 1.32-1.17 (m, 3H), 1.10 (d, *J* = 7.07 Hz, 18H). **^{13}C NMR (101 MHz, *CDCl$_3$*)** δ 157.40, 132.06, 125.54, 117.60, 90.52, 90.48, 79.57, 27.68, 19.58, 18.13, 13.42, 12.87. **HRMS (EI)** m/z calcd for $C_{20}H_{34}O_1Si$ = 318.2379, found mass = 318.2380.

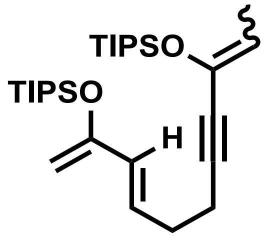


Triisopropyl(3-methyldeca-1,3,9-trien-7-yn-2-yl]oxy})silane (4.65x)

(Guillaume Revol post-Doctorate work)

Diene-enyne (**4.65x**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

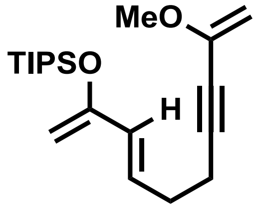
IR (neat, cm^{-1}) ν max 2945.1, 2866.8, 1587.3, 1297.8, 1020.0, 678.5. **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ 6.16 (t, *J* = 6.51 Hz, 1H), 5.75 (tdd, *J* = 17.52, 11.01, 1.95 Hz, 1H), 5.53 (dd, *J* = 17.51, 2.28 Hz, 1H), 5.37 (dd, *J* = 11.00, 2.29 Hz, 1H), 4.39 (d, *J* = 1.09 Hz, 1H), 4.27 (s, 1H), 2.41-2.35 (m, 4H), 1.77 (d, *J* = 0.81 Hz, 3H), 1.32-1.17 (m, 3H), 1.10 (d, *J* = 7.07 Hz, 18H). **^{13}C NMR (101 MHz, *CDCl$_3$*)** δ 157.40, 132.06, 125.54, 117.60, 90.52, 90.48, 79.57, 27.68, 19.58, 18.13, 13.42, 12.87. **HRMS (EI)** m/z calcd for $C_{20}H_{34}O_1Si$ = 318.2379, found mass = 318.2380.



Bis(Triisopropyl)[(3-methyldeca-1,3,9-trien-7-yn-2,9-diyl)oxy]silane (4.81)

Diene-enyne (**4.81**) was prepared according to the **general procedure I** silyl enol ether formation and isolated as a clear oil.

^{1}H-NMR (400 MHz; CDCl$_3$): δ 6.14-6.04 (m, 1H), 5.96-5.89 (m, 1H), 5.18 (q, J = 7.1 Hz, 0.25*1H), 4.93 (q, J = 6.9 Hz, 0.75*1H), 4.25 (s, 1H), 4.19 (s, 1H), 2.40-2.28 (m, 4H), 1.68 (d, J = 7.1 Hz, 0.25*3H), 1.63 (d, J = 6.9 Hz, 0.75*3H), 1.32-1.17 (m, 6H), 1.11 (d, J = 7.1 Hz, 36H). **^{13}C NMR (101 MHz; CDCl$_3$):** δ 155.2 (C$_{quat}$), 134.5 (C$_{quat}$*0.25), 134.4 (C$_{quat}$*0.75), 129.3 (CH), 120.2 (CH), 112.7 (CH*0.25), 112.4 (CH*0.75), 93.8 (CH$_2$), 86.5 (C$_{quat}$), 79.6 (C$_{quat}$), 31.2 (CH$_2$), 19.4 (CH$_2$), 18.2 (CH$_3$), 18.1 (CH$_3$*12), 12.9 (CH$_3$*6). **HRMS (EI**) m/z calcd for $C_{29}H_{54}O_2Si_2$ 490.3662, found 490.3694.

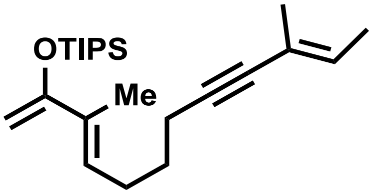


Triisopropyl[(9-methoxyldeca-1,3,9-trien-7-yn-2-yl)oxy]silane (4.83)

Diene-enyne (**4.83**) was prepared according to the **general procedure I** silyl enol ether formation and isolated as a clear oil.

Synthesized according to general procedure of Sonagashira reaction and isolated as a clear oil.

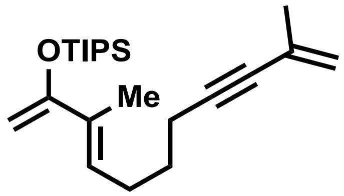
^{1}H-NMR (400 MHz; CDCl$_3$): δ 6.16-6.07 (m, 1H), 5.97-5.90 (m, 1H), 4.45 (d, J = 2.2 Hz, 1H), 4.40 (d, J = 2.1 Hz, 1H), 4.25 (s, 1H), 4.20 (s, 1H), 3.56 (s, 3H), 2.43-2.31 (m, 4H), 1.27-1.20 (m, 3H), 1.10 (d, J = 7.1 Hz, 18H). **^{13}C NMR (101 MHz; CDCl$_3$):** δ 155.2 (C$_{quat}$), 145.5 (C$_{quat}$), 129.4 (CH), 129.1 (CH), 94.0 (CH$_2$), 91.8 (CH$_2$), 88.2 (CH$_3$), 77.2 (C$_{quat}$), 55.5 (C$_{quat}$), 31.0 (CH$_2$), 19.3 (CH$_2$), 18.2 (CH$_3$), 12.9 (CH). **HRMS (EI**) m/z calcd for $C_{20}H_{34}OSi$ 334.2328, found 334.2302



Triisopropyl[(3,11,13-trimethylundeca-1,3,10-trien-8-yn-2-yl)oxy]silane (4.87)

Diene-enyne (**4.87**) was prepared according to the **general procedure F** Sonagashira reaction followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

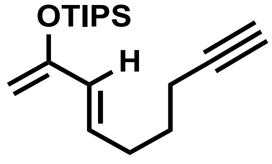
^{1}H-NMR (400 MHz; CDCl$_3$): δ 6.12-6.07 (m, 1H), 5.82 (qd, *J* = 7.0, 1.5 Hz, 1H), 4.40 (s, 1H), 4.26 (s, 1H), 2.36 (s, 4H), 2.21-2.17 (m, 2H), 1.75 (t, *J* = 1.3 Hz, 3H), 1.66 (dd, *J* = 7.0, 1.0 Hz, 3H), 1.50-1.41 (m, 2H), 1.27-1.19 (m, 3H), 1.09 (d, J = 7.1 Hz, 18H), 0.93 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (101 MHz; CDCl$_3$):** δ 156.9 (C$_{quat}$), 137.0 (C$_{quat}$), 130.9 (CH), 126.7 (CH), 118.9 (C$_{quat}$), 90.4 (CH$_2$), 85.8 (C$_{quat}$), 83.8 (C$_{quat}$), 29.8 (CH$_2$), 28.0 (CH$_2$), 22.9 (CH$_2$), 19.5 (CH$_2$), 18.21 (CH$_3$x6), 17.9 (CH$_3$), 17.3 (CH$_3$), 14.2 (CH$_3$), 12.4 (CHx3. **HRMS (EI**) m/z calcd for $C_{24}H_{42}OSi$ [$(M-C_3H_7)^+$] 331.2457, found 331.2443.



Triisopropyl[(3,11-dimethylundeca-1,3,10-trien-8-yn-2-yl)oxy]silane (4.87b)

Diene-enyne (**4.87b**) was prepared according to the **general procedure F** Sonagashira reaction followed followed by the **general procedure I** silyl enol ether formation and isolated as a clear oil.

^{1}H-NMR (400 MHz; CDCl$_3$): δ 6.08 (t, J = 7.5 Hz, 1H), 5.20 (br, 1H), 5.14 (q, J = 1.7 Hz, 1H), 4.51 (d, J = 1.0 Hz, 1H), 4.24 (s, 1H), 2.31 (t, J = 7.1 Hz, 2H), 2.25 (quin, J = 7.5 Hz, 2H), 1.87 (t, J = 1.3 Hz, 3H), 1.78 (s, 3H), 1.63 (quin, J = 7.3 Hz, 2H), 1.28-1.20 (m, 3H), 1.10 (d, J = 7.1 Hz, 18H). **^{13}C NMR (101 MHz; CDCl$_3$):** δ 157.7 (C$_{quat}$), 131.9 (C$_{quat}$), 127.5 (CH), 127.3 (C$_{quat}$), 120.4 (CH$_2$), 90.4 (CH$_2$), 89.3(C$_{quat}$), 82.2 (C$_{quat}$), 28.7 (CH$_2$), 27.5 (CH$_2$), 24.0 (CH$_3$), 18.9 (CH$_2$), 18.2 (CH$_3$), 13.4 (CH$_3$), 12.9 (CH). **HRMS (EI**) m/z calcd for $C_{22}H_{38}OSi$ [$(M-C_3H_7)^+$] 303.2144, found 303.2156.



Triisopropyl[undeca-1,3-dien-8-yn-2-yl)oxy]silane (4.X1)

Diene-enyne (**4.X1**) was prepared according to the **general procedure I** silyl enol ether formation and isolated as a clear oil.

^{1}H NMR (400MHz, CDCl$_3$) δ 6.03 (ddd, J = 15.6 Hz, 7.7 Hz, 7.7 Hz, 1H), 5.89 (ddd, J = 15.0 Hz, 1.2 Hz, 1.2 Hz, 1H), 4.22 (s, 1H), 4.18 (s, 1H), 2.25-2.16 (m, 4H), 1.95 (t, J = 2.6 Hz, 1H), 1.64 (quin, J = 7.3 Hz, 2H), 1.28-1.18 (m, 3H), 1.10 (d, J = 6.8 Hz, 18H); **^{13}C NMR (101MHz, CDCl$_3$)** δ 155.3

(C_{quat}), 130.3 (CH), 129.0 (CH), 84.5 (C_{quat}), 68.6 (CH), 46.4 (CH_2), 31.1 (CH_2), 28.1 (CH_2), 18.2 (CH_3), 12.9 (CH) **HRMS (EI)** m/z calcd for $C_{18}H_{32}OSi$ [$(M)^+$] 292.2222, found 295.1518

7.9 Detailed Experimental: Synthesis of steroid-related s scaffold from linear precursor

General Procedure J and K: Diels-Alder/ Gold(I)-Catalyzed Carbocyclization/ Diels-Alder Sequence

General Precaution

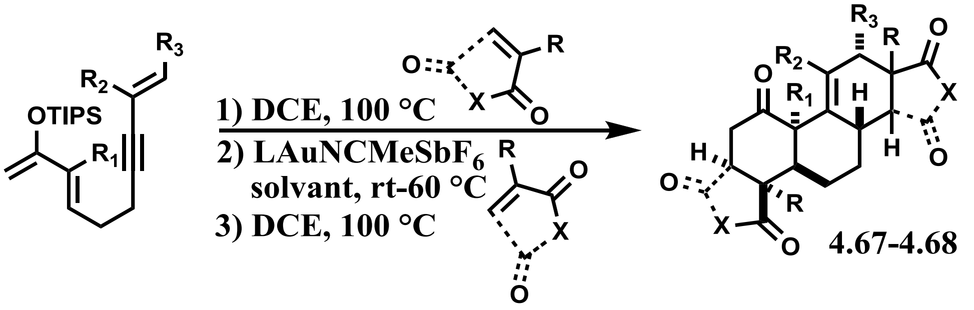
Be careful to don't have trace of silver salt in gold(I) catalyst, if not hydrolysis of silylenol ether will happen.. Be carefull to do not extended the heating time further than 24 hrs for the first Diels-Alder reaction or isomerisation of the silylenol ether can happen. In some case the diastereoselectivity of the Diels-Alder reaction can be improved with longer reaction time. If phenyl maleimide is used in the first Diels-Alder, the reaction was performed at rt for 18hr instead of 100°C for 18 hr.

General Procedure J

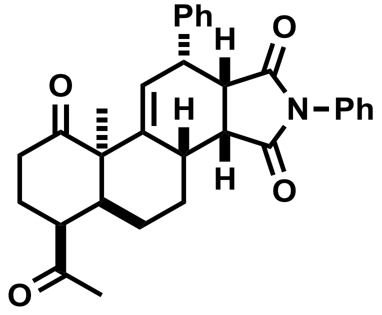
In a sealed tube, the dienophile (1-5 eq.) was added to a solution of the diene (1 eq.) in DCE (10 mL/mmol). The tube was heated at 100°C for 18 hrs, then cooled down too room temperature. The solvent is then exchange for acetone/methanol (10/1), the gold catalyst ([Au(Me_4XPhos),SbF_6], 5 mol%) was added to the solution and the reaction was stirred at room temperature for 18hrs. The solvent is then switch back to DCE, the second dienophile (2-10 eq.) is added and the solution heated at 60°C for 18hrs to 48hrs. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (80 :20 to 40 :60)) to give the expected products.

General Procedure K

In a sealed tube, the dienophile (1-5 eq.) was added to a solution of the diene (1 eq.) in DCE (10 mL/mmol). The tube was heated at 100°C for 18 hrs, then cooled down too room temperature. The solvent is then exchange for acetone, diphenylsulfoxide (2 eq.) and the gold catalyst ([Au(Me$_4$XPhos),SbF$_6$], 5 mol%) was added to the solution, then the reaction was stirred at room temperature for 18hrs. The solvent is then switch back to DCE, the second dienophile (2-10 eq.) is added and the solution heated at 60°C for 18hrs to 48hrs. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (80:20 to 40:60)) to give the expected products. In some case the two dienophiles, the first and the second are the same



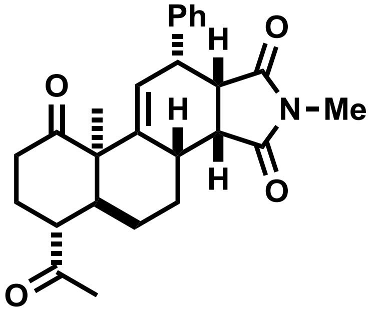
Scheme 7.12 *Synthesis of steroid-related scaffold from linear precursor*



Tetracycle (4.67s) (Guillaume Revol post-Doctorate work)

Tetracycle (**4.67s**) was synthesized according to the **general procedure J** employing silyl enol ether (**4.65s**) (100 mg, 0.25 mmol), 3-buten-2-one (102 µL, 1.25 mmol), [AuMe$_4$Xphos,SbF$_6$] (12 mg ,13*10^{-3} mmol) and *N*-phenylmaleimide (86 mg, 0.50 mmol), acetone (1 mL) and methanol (0.1 mL) as solvent to gives the expected product (**4.67s**) (52 mg, 43%) as a sole diastereoisomer. Three other minor diastereoisomers present in the crude couldn't be obtained clean for characterization.

IR (neat, cm^{-1}) ν max 3066.4, 2945.1, 2882.5, 1771.2, 1712.51, 1493.39, 1379.9, 1180.4, 734.3 **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ 7.49-7.31 (m, 7H), 7.28 (m, 3H), 5.90 (t, *J* = 2.64 Hz, 1H), 3.46 (m, *J* = 9.50, 2.59, 1.39 Hz, 1H), 3.29 (t, *J* = 9.52 Hz, 1H), 3.23-3.17 (m, 1H), 2.94 (dd, *J* = 10.43, 9.77 Hz, 1H), 2.67-2.43 (m, 3H), 2.40-2.29 (m, 1H), 2.21 (s, 3H), 2.21-2.08 (m, 3H), 1.60-1.49 (m, 2H), 1.48 (s, 3H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 212.55, 176.85, 176.70, 143.82, 142.97, 131.68, 130.44, 128.97, 128.71, 128.55, 128.37, 127.01, 126.37, 52.71, 50.19, 48.49, 45.79, 43.15, 41.00, 38.19, 36.70, 28.21, 24.73, 22.72, 22.69, 21.76: **HRMS** calculated for [C31H31NO4] = 481.2253, found mass = 481.2276.



Tetracycle (4.67s1) (Guillaume Revol post-Doctorate work)

Tetracycle (**4.67s1**) was synthesized according to the **general procedure J** employing silyl enol ether (**4.65s**) (102 μL, 1.25 mmol), [AuMe$_4$tBuXphos,SbF$_6$] (12 mg ,13*10^{-3} mmol) and *N*-methylmaleimide (56 mg, 0.50 mmol) and DCE (1 mL) and acetone with 10% methanol (1 mL) as successive solvent to gives expected product (**4.67s1**) as major diastereoisomer (30 mg, 29%) and a mixture of the four possible diastereoisomers (33 mg, 31%), Only Major diastereoisomer could be characterized.

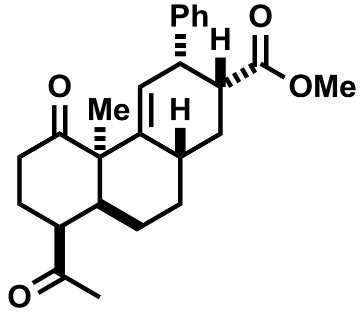
Major Diastereoisomer

IR (neat, cm^{-1}) ν max 2952.9, 1774.9, 1700.6, 1434.7, 1278.2, 707.28. **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ 7.36 (t, *J* = 7.25 Hz, 2H), 7.34-7.27 (m, 1H), 7.26-7.19 (m, 2H), 5.81-5.73 (m, 1H), 3.63-3.49 (m, 1H), 3.28 (dd, *J* = 8.21, 6.60 Hz, 1H), 3.18 (dd, *J* = 8.36, 6.41 Hz, 1H), 2.87-2.77 (m, 2H), 2.81 (s, 3H), 2.66-2.49 (m, 2H), 2.34 (td, *J* = 14.60, 4.11 Hz, 1H), 2.22-2.20 (m, 1H), 2.20 (s, 3H),2.13-2.02 (m, 2H), 1.78 (ddd, *J* = 24.70, 13.27, 4.22 Hz, 1H), 1.56-1.40 (m, 1H), 1.19 (s, 3H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 210.36, 209.93, 177.81, 175.80, 142.53, 138.54, 128.79, 128.29, 127.25, 126.37, 53.12, 52.60, 46.21, 46.09, 43.56, 42.32, 37.25, 32.62, 29.72, 28.17, 28.15, 25.07, 24.47, 22.60, 19.80: **HRMS** calculated mass for M($C_{26}H_{29}NO_4$) = 419.2096, found mass = 419.2131.

Mixture of Diastereoisomer

IR (neat, cm^{-1}) ν max 2933.3, 2882.5, 1775.1, 1704.7(bs), 1434.7(b), 379.9, 1289.9, 730.4.

HRMS calculated mass for M($C_{26}H_{29}NO_4$) = 419.2096, found mass = 419.2109.

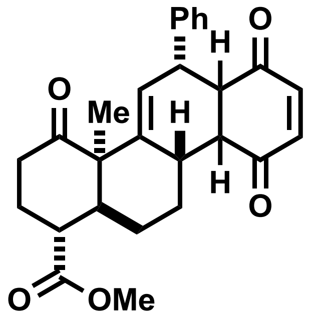


Tetracycle (4.67s2) (Guillaume Revol post-Doctorate work)

Tetracycle (**4.67s2**) was synthesized according to the **general procedure J** employing silyl enol ether (**4.65s)** (50 mg, 0.13 mmol), 3-buten-2-one (21 µL, 0.26 mmol), [AuMe$_4$tBuXphos,SbF$_6$] (6 mg ,7*10^{-3} mmol) and methyl acrylate (58 µL, 0.65 mmol), DCE (1 mL) and acetone with 10% methanol (1 mL) as successive solvent to gives expected product (**4.67s2**) as a mixture of 4 diastereoisomers (27 mg, 57%, d.r. = 6:1.7:1:1).

Major Diastereoisomer (4.67s2)

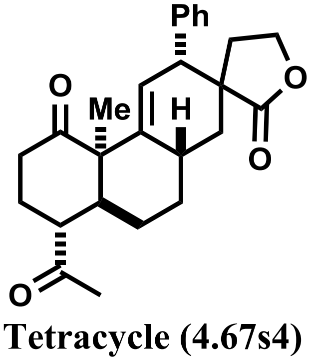
IR (neat, cm^{-1}) ν max 2929.4, 2866.8, 1736.0, 1708.6, 1454.26, 1164.7, 720.46. **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ 7.41-7.12 (m, 5H), 5.38 (dd, *J* = 2.78, 2.07 Hz, 1H), 3.74 (td, *J* = 6.54, 2.61 Hz, 1H), 3.59 (s, 3H), 2.96-2.83 (m, 1H), 2.64-2.50 (m, 3H), 2.51-2.38 (m, 3H), 2.21 (s, 3H), 1.98 (ddd, *J* = 13.40, 9.12, 5.72 Hz, 1H), 1.69-1.60 (m, 1H), 1.57-1.44 (m, 2H), 1.41 (s, 3H). **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 213.10, 208.99, 175.35, 143.89, 139.80, 128.45, 128.13, 126.59, 125.57, 54.02, 51.62, 48.48, 44.97, 43.96, 43.18, 35.57, 30.18, 28.61, 28.55, 27.93, 24.79, 21.60, 21.56. **HRMS** calculated mass for [$C_{25}H_{30}O_4$] = 394.2144, found 394.2173.



Tetracycle (4.67s3) (Guillaume Revol post-Doctorate work)

Tetracycle (**4.67s3**) was synthesized according to the **general procedure K** employing silyl enol ether (**4.65s)** (100 mg, 0.25 mmol), 3-buten-2-one (102 µL, 1.25 mmol), [AuMe$_4$tBuXphos,SbF$_6$] (12 mg ,13*10^{-3} mmol) and benzoquinone (54 mg, 0.50 mmol) and acetone (1 mL) as solvent to gives expected product (**4.67s3**) as a sole diastereoisomer (30 mg, 28%). Other diastereoisomer are observed but couldn't be characterized.

IR (neat, cm^{-1}) ν max.2945.06, 1735.99, 1704.68, 1653.8, 1509.0, 1207.8, 701.1. **^{1}H NMR (400 MHz, *CDCL$_3$*)** δ 7.36 (s, 2H), 7.35 (d, *J* = 0.88 Hz, 2H), 7.29-7.22 (m, 1H), 6.74 (d, *J* = 10.31 Hz, 1H), 6.64 (dd, *J* = 10.29, 1.04 Hz, 1H), 5.55 (dd, *J* = 4.41, 2.18 Hz, 1H), 4.14 (dd, *J* = 6.14, 4.06 Hz, 1H), 3.72 (s, 3H), 3.17-3.10 (m, 2H), 2.81 (ddd, *J* = 8.36, 4.80, 0.88 Hz, 1H), 2.65-2.46 (m, 4H), 2.32-2.19 (m, 1H), 2.19-2.09 (m, 1H), 1.84-1.72 (m, 2H), 1.56 (m, 2H), 1.49 (s, 3H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 212.28, 199.62, 197.95, 174.14, 142.32, 140.00, 139.21, 138.44, 126.74, 125.09, 54.16, 53.65, 52.01, 50.59, 42.39, 40.66, 39.68, 36.10, 31.46, 25.91, 23.56, 21.033: **HRMS** calculated mass for M($C_{21}H_{30}O_3$) = 432.1937, found mass = 432.1938. **Fp** = 140-145°C.



Tetracycle (4.67s4) (Guillaume Revol post-Doctorate work)

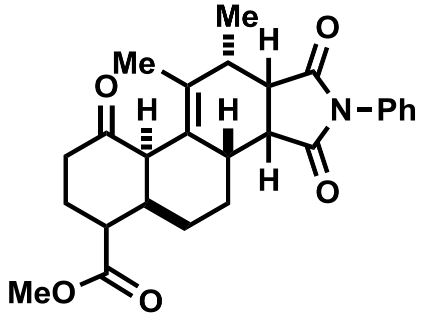
Tetracycle (**4.67s4**) was synthesized according to the **general procedure J** employing silyl enol ether (**4.65s)** (100 mg, 0.25 mmol), 3-buten-2-one (102 µL, 1.25 mmol), [AuMe$_4$tBuXphos,SbF$_6$] (12 mg ,13*10^{-3} mmol) and 3-methylenetetrahydrofuran-2-one (125 mg, 1.25 mmol) and DCE (1 mL) and acetone with 10% methanol (1 mL) as successive solvent to gives expected product (**4.67s3**) as a mixture of two diastereoisomers (41 mg, 33%, d.r. = 2:1).

Major Diastereoisomer (4.67s4)

IR (neat, cm^{-1}) ν max 2925.3, 2866.8, 1767.3, 1704.7, 1446.4,.1372.1, 1176.5, 1027.8, 734.3: **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ 7.40-7.31 (m, 5H), 5.51 (dd, *J* = 3.53, 2.75 Hz, 1H), 4.09-3.99 (m, 1H), 3.65-3.56 (m, 2H), 3.15 (td, *J* = 12.54, 4.44 Hz, 1H), 2.66-2.58 (m, 1H), 2.59-2.50 (m, 2H), 2.44 (ddd, *J* = 15.35, 6.33, 2.69 Hz, 1H), 2.22 (s, 3H), 2.24-2.17 (m, 3H), 2.04 (dd, *J* = 13.63, 6.29 Hz, 1H), 1.72-1.61 (m, 4H), 1.59 (dd, *J* = 7.41, 6.35 Hz, 1H), 1.54 (s, 3H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 212.97, 209.37, 180.49, 140.57, 139.54, 129.54, 128.42, 127.29, 125.22, 65.23, 53.71, 48.88, 46.96, 44.89, 41.75, 36.29, 34.49, 33.50, 29.52, 28.80, 26.60, 25.70, 22.50, 21.46.:**HRMS** calculated mass for M(C$_{26}$H$_{30}$O$_4$) = 406.2144, found mass = 406.2140.

Minor Diastereoisomer (4.67s4)

^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.33-7.27 (m, 3H), 7.15 (dd, *J* = 7.80, 1.41 Hz, 1H), 5.41 (dd, *J* = 3.60, 2.25 Hz, 1H), 4.06 (td, *J* = 9.17, 7.38 Hz, 1H), 3.62 (dd, *J* = 3.39, 2.63 Hz, 1H), 3.62-3.55 (m, 1H), 2.86 (dt, *J* = 8.33, 4.75 Hz, 1H), 2.74 (ddd, *J* = 14.36, 10.92, 5.44 Hz, 1H), 2.66-2.57 (m, 2H), 2.53-2.45 (m, 2H), 2.43-2.33 (m, 1H), 2.27 (s, 3H), 2.17-2.07 (m, 3H), 1.57-1.49 (m, 4H), 1.35 (s, 3H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 211.27, 210.62, 180.33, 141.68, 140.32, 129.20, 128.44, 127.39, 123.43, 65.12, 54.50, 53.75, 46.57, 44.87, 44.02, 42.83, 36.87, 34.56, 33.68, 31.21, 29.28, 24. 67.



Tetracycle (4.67t) (Guillaume Revol post-Doctorate work)

Tetracycle (**4.67t**) was synthesized according to the **general procedure J** employing silyl enol ether (**4.65t)** (50 mg, 0.15 mmol), methylacrylate (68 μL, 0.75 mmol), [AuJohnphos,SbF$_6$] (6 mg, 7.5*10^{-3}mmol) and *N*-phenylmaleimide (61 mg, 0.30 mmol), DCE (0.5 mL) and acetone/methanol (10/1) (0.5

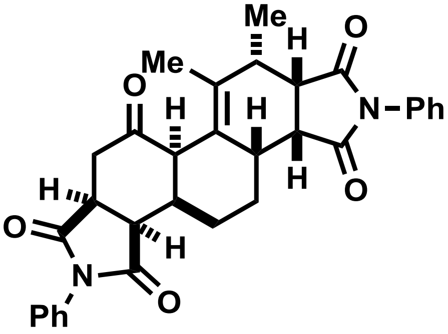
mL) as successive solvent to gives expected product **(4.67t)** as major diastereoisomer (17 mg, 26%) contaminated by hydrolyzed first [4+2] adduct and minor diastereoisomer (17 mg, 26%).

Major Diastereoisomer (4.67t)

IR (neat, cm^{-1}) ν max 2956.8, 2925.6, 1771.4, 1712.5, 1383.8, 1192.1, 734.3. **^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm** 7.45 (t, *J* = 7.53 Hz, 2H), 7.40-7.33 (m, 1H), 7.21 (dd, *J* = 7.47, 1.41 Hz, 2H), 3.74-3.68 (m, 1H), 3.71 (s, 3H), 3.32 (t, *J* = 8.87 Hz, 1H), 3.25 (dd, *J* = 8.91, 6.40 Hz, 1H), 3.04 (td, *J* = 12.02, 4.36 Hz, 1H), 2.75-2.65 (m, 2H), 2.65-2.52 (m, 2H), 2.48 (ddd, *J* = 14.48, 4.71, 2.72 Hz, 1H), 2.44-2.29 (m, 2H), 2.22-2.09 (m, 2H), 1.78-1.61 (m, 2H), 1.66 (s, 3H), 1.58-1.47 (m, 1H) ,1.18 (d, *J* = 7.18 Hz, 3H). **^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm** 208.88, 177.36, 177.33, 173.32, 132.87, 129.16, 129.09, 128.46, 126.55, 126.52, 54.24, 51.96, 45.53, 44.29, 42.68, 41.00, 40.30, 35.43, 33.55, 28.49, 24.41, 23.45, 17.09, 15.72. **HRMS** calculated mass for [$C_{26}H_{29}NO_5$] = 435.2046, found = 435.2072.

Minor Diastereoisomer (4.67t)

IR (neat, cm^{-1}) ν max 2965.4, 2937.4, 1773.9, 1710.3, 1181.9, 746.7. **^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm** 7.51-7.41 (m, 2H), 7.41-7.34 (m, 1H), 7.23 (dd, *J* = 7.33, 1.42 Hz, 1H), 3.95 (d, *J* = 6.08 Hz, 1H), 3.78 (s, 3H), 3.70 (d, *J* = 9.28 Hz, 1H), 3.62-3.53 (m, 1H), 3.58 (td, *J* = 13.10, 6.06 Hz, 1H), 3.34 (t, *J* = 9.14 Hz, 1H), 3.26 (dd, *J* = 9.00, 6.31 Hz, 1H), 2.84-2.73 (m, 1H), 2.74-2.65 (m, 1H), 2.66-2.50 (m, 4H), 2.43-2.29 (m, 2H), 2.22-2.08 (m, 1H), 1.72 (d, *J* = 7.50 Hz, 1H), 1.67 (s, 3H), 1.17 (d, *J* = 7.15 Hz, 3H). **^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm** 209.93, 177.48, 177.40, 174, 66, 132.94, 131.04, 129.31, 129.10, 128.95, 128.47, 126.56, 126.47, 124.78, 52.09, 51.46, 44.25, 44.16, 42.26, 40.73, 38.85, 35.55, 33.40, 29.79, 28.98, 24.15, 17.17, 15.68. **HRMS** calculated mass for [$C_{26}H_{29}NO_5$] = 435.2046, found = 435.2031.



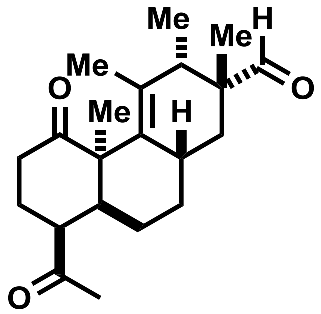
Tetracycle (4.68t) (Guillaume Revol post-Doctorate work) etracycle (**4.68t**) was synthesized according to the **general procedure K** employing silyl enol ether (**4.65t)** (100 mg, 0.30 mmol), *N*-phenylmaleimide (156 mg, 0.90 mmol), [AuJohnphos,SbF_6] (12 mg, 15*10^{-3} mmol), diphenylsulfoxide (121 mg, 0.60 mmol) and acetone (1 mL) to gives expected product **(4.68t)** as a mixture major and minor diastereoisomer (136 mg, 81%, d.r. = 4.6:1).

Major Diastereoisomer (4.68t)

IR (neat, cm^{-1}) ν max for the mixture, 3066.36, 2968.5, 2933.8, 1771.2, 1704.7, 1497.3, 1383.8, 1180.4, 734.3. **^{1}H NMR (400 MHz, *$CDCl_3$*)** δ 7.53-7.35 (m, 6H), 7.29 (dd, *J* = 7.25, 1.29 Hz, 2H), 7.23 (dd, *J* = 7.32, 1.23 Hz, 2H), 3.55-3.51 (m, 1H), 3.48 (dd, *J* = 6.61, 5.97 Hz, 1H), 3.30 (m, 2H), 2.96 (dd, *J* = 11.47, 8.46 Hz, 1H), 2.79-2.65 (m, 3H), 2.50 (t, *J* = 9.78 Hz, 1H), 1.98 (m, 1H), 1.81 (s, 3H), 1.72-1.59 (m, 2H), 1.53 (m, 1H), 1.31-1.18 (m, 1H), 1.11 (d, *J* = 7.12 Hz, 3H): **^{13}C NMR (400 MHz, *$CDCl_3$*)** δ ppm 207.17, 177.40, 177.26, 176.85, 175.94, 133.69, 131.76, 131.44, 129.37, 129.28, 129.21, 128.97, 128.63, 126.52, 126.28, 52.76, 43.84, 43.11, 39.86, 39.02, 36.93, 36.31, 35.56, 35.63, 33.63, 29.19, 25.98, 18.02, 15.85: **HRMS** for the mixture, calculated mass for $[C_{33}H_{32}N_2O_5]$ = 522.2155, found mass = 522.2267. **Fp** = 258-266°C.

Minor Diastereoisomer(4.68t)

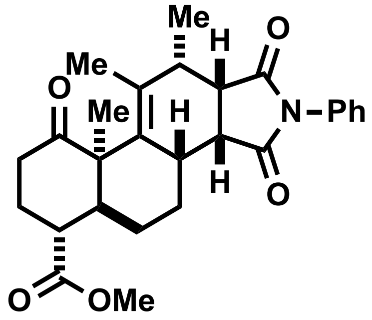
^{1}H NMR (400 MHz, *$CDCl_3$*) δ 7.56-7.35 (m, 5H), 7.34-7.29 (m, 2H), 7.20 (dd, *J* = 7.96, 1.82 Hz, 2H), 7.13 (m, 1H), 3.49-3.44 (m, 1H), 3.41 (dd, *J* = 9.27, 6.21 Hz, 1H), 3.01 (dd, *J* = 13.16, 11.17 Hz, 1H), 2.92-2.82 (m, 1H), 2.39-2.28 (m, 1H), 2.27-2.12 (m, 1H), 2.11-2.05 (m, 2H), 1.95-1.87 (m, 1H), 2.81 (m, 1H), 1.55 (s, 3H), 1.48 (dd, *J* = 8.18, 4.33 Hz, 1H), 1.31-1.19 (m, 3H), 1.24 (d, *J* = 7.20 Hz, 3H). **^{13}C NMR (400 MHz, *$CDCl_3$*)** δ 203.74, 177.85, 177.40, 177.17, 175.10, 138.27, 131.74, 131.48, 129.43, 129.18, 128.97, 128.55, 126.45, 126.19, 52.17, 44.89, 43.25, 42.41, 37.98, 36.82, 35.72, 35.12, 31.05, 26.76, 24.50, 17.70, 16.06.



Tetracycle (4.67u1) (Guillaume Revol post-Doctorate work)

Tetracycle (**4.67u1**) was synthesized according to the **general procedure K** employing silyl enol ether (**4.65u)** (50 mg, 0.14 mmol), 3-buten-2-one (58 µL, 0.70 mmol), [AuMe$_4$tBuXphos,SbF$_6$] (7 mg, 710^{-3} mmol), diphenylsulfoxyde (57 mg, 0.28 mmol) and methacrolein (58 µL, 0.70 mmol) and DCE (0.5 mL) and acetone (0.5 mL) as successive solvent to gives expected product **(4.67u1*)*** as a sole diastereoisomer (20 mg, 43%), contaminated by 13% of diphenylsulphoxyde.

IR (neat, cm^{-1}) ν max 2929.4, 2874.6, 1700.8, 1462.1, 1376.0, 734.3: **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ 9.54 (s, 1H), 2.83 (ddd, *J* = 11.95, 5.94, 3.89 Hz, 1H), 2.59 (dd, *J* = 9.91, 6.50 Hz, 1H), 2.55 (d, *J* = 8.36 Hz, 1H), 2.48 (ddd, *J* = 11.77, 9.11, 5.49 Hz, 1H), 2.28-2.15 (m, 1H), 2.14 (s, 3H), 2.13-1.95 (m, 1H), 1.91-1.81 (m, 1H), 1.79-1.69 (m, 1H), 1.66-1.52 (m, 1H), 1.49 (s, 3H), 1.38 (s, 3H), 1.07 (d, *J* = 6.83 Hz, 3H), 1.02 (s, 3H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 213.64, 208.77, 206.40, 134.35,131.08, 129.35, 129.15, 124.81, 55.51, 47.99, 46.91, 46.41, 37.48, 35.78, 33.05, 32.27, 28.36, 25.22, 24.81, 21.88, 20.13, 20.05, 19.20, 19.16: **HRMS** calculated mass for [$C_{21}H_{30}O_3$] = 330.2195, found = 330.2181.



Tetracycle (4.67u2) (Guillaume Revol post-Doctorate work)

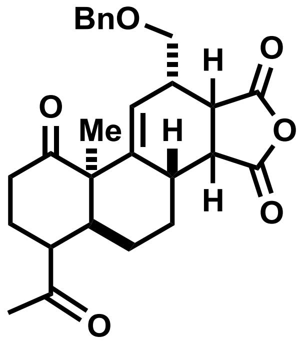
Tetracycle (**4.67u2**) was synthesized according to the **general procedure J** employing silyl enol ether (**4.65u)** (50 mg, 0.14 mmol), 3-buten-2-one (60 µL, 0.72 mmol), [AuMe$_4$tBuXphos,SbF$_6$] (7 mg, 710^{-3} mmol) and *N*-phenylmaleimide (48 mg, 0.28 mmol), DCE (0.5 mL) and acetone/methanol (10/1) as successive solvent to gives expected product **(4.67u2)** a mixture of diastereoisomer (33 mg, 55%, dr = 4.5:1).

Major Diastereoisomer (4.67u2)

IR (neat, cm^{-1}) ν max 2937.2, 2878.5, 1771.2, 1708.6, 1493.4, 1383.8, 1184.3, 734.3.**^{1}H NMR (400 MHz, *CDCl$_3$*)** δ 7.52-7.41 (m, 2H), 7.38 (t, *J* = 7.45 Hz, 1H), 7.31-7.24 (m, 2H), 3.06 (td, *J* = 12.57, 4.69 Hz, 1H), 2.94 (dd, *J* = 8.61, 3.49 Hz, 1H), 2.88 (dd, *J* = 8.62, 4.09 Hz, 1H), 2.72-2.59 (m, 4H), 2.44-2.31 (m, 1H), 2.19 (s, 3H), 2.15-2.07 (m, 2H), 2.07-1.95 (m, 2H), 1.58 (s, 3H), 1.52 (s, 3H), 1.38-1.27 (m, 2H), 1.33 (d, *J* = 7.09 Hz, 3H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 212.30, 208.68, 178.80, 177.78, 133.24, 130.11, 129.10, 128.43, 126.51, 126.18, 55.17, 48.27, 46.09, 45.98, 43.07, 36.28, 34.95, 31.84, 30.00, 28.48, 24.80, 23.51, 21.48, 21.37, 19.62: **HRMS** calculated mass for [$C_{27}H_{31}NO_4$] = 433.2253, found mass = 433.2240.

Minor Diastereoisomer (4.67u2)

^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.52-7.41 (m, 2H), 7.38 (t, *J* = 7.45 Hz, 1H), 7.13 (dd, *J* = 7.26, 1.28 Hz, 2H), 3.14 (dd, *J* = 8.90, 4.79 Hz, 1H), 3.08 (m, 1H), 2.98-2.91 (m, 1H), 2.79-2.59 (m, 2H), 2.51 (ddd, *J* = 12.61, 4.96, 2.48 Hz, 2H), 2.45 (dd, *J* = 6.60, 4.29 Hz, 1H), 2.42-2.33 (m, 2H), 2.16 (s, 3H), 1.72-1.60 (m, 2H), 1.58 (s, 3H), 1.52 (s, 3H), 1.37-1.27 (m, 5H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 209.07, 207.25, 178.08, 176.72, 133.19, 131.87, 130.11, 129.17, 128.57, 126.51, 54.12, 49.91, 48.97, 45.66, 45.22, 37.59, 36.50, 35.81, 29.69, 28.29, 25.70, 25.48, 23.88, 22.67, 17.72.



Tetracycle (4.67v1) (Guillaume Revol post-Doctorate work)

Tetracycle (**4.67v1**) was synthesized according to the **general procedure J** employing silyl enol ether (**4.65v**) (50 mg, 0.11 mmol), 3-buten-2-one (46 μL, 0.56 mmol), [AuMe$_4$tBuXphos,SbF$_6$] (6 mg, 6*10^{-3} mmol)and *N*-phenylmaleimide (38 mg, 0.22 mmol), acetone (1 mL) and methanol (0.1 mL) as solvent to gives expected product (**4.67v1**) as endo diastereoisomer (13 mg, 25%) and exo diastereoisomer of last [4+2] (20 mg, 38%). These products aren't very stable if there are not kept at 0°C.

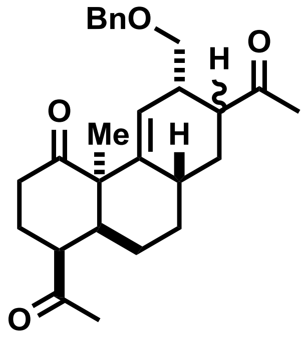
Major Diastereoisomer (4.67v1)

IR (neat, cm^{-1}) ν max 2930.0, 2855.6, 1779.6, 1705.2, 1462.6, 1372.6, 1204.4, 738.74**. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm** 7.39-7.25 (m, 5H), 5.59 (dd, *J* = 4.14, 1.94 Hz, 1H), 4.52 (d, *J* = 11.71 Hz, 1H), 4.47 (d, *J* = 11.85 Hz, 1H), 3.76 (dd, *J* = 15.95, 6.76 Hz, 1H), 3.69 (dd, *J* = 9.30, 5.35 Hz, 1H), 3.49

(dd, *J* = 9.36, 7.46 Hz, 1H), 3.39 (dd, *J* = 9.32, 8.13 Hz, 1H), 3.25-3.05 (m, 2H), 2.90-2.78 (m, 1H), 2.64-2.43 (m, 3H), 2.36 (ddd, *J* = 15.59, 6.09, 2.31 Hz, 1H), 2.18 (s, 3H), 2.13-2.05 (m, 4H), 1.46 (s, 3H). **^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm** .211.92, 208.80, 171.66, 171.39, 141.91, 137.67, 128.41, 128.04, 127.85, 123.38, 73.15, 69.51, 55.45, 48.78, 46.92, 43.91, 41.14, 36.04, 35.22, 33.98, 28.25, 27.59, 24.24, 23.77, 21.80. **HRMS** calculated mass for M-Bn($C_{25}H_{26}NO_4$) = 359.1495, found mass M = 359.1499. **Fp** = 111-115°C.

Minor Diastereoisomer (4.67v1)

IR (neat, cm^{-1}) ν max 2928.8, 2858.3, 1774.5, 1700.1, 1445.8, 1359.7, 733.0. **^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm** 7.38-7.31 (m, 4H), 7.31-7.25 (m, 1H), 5.87 (t, *J* = 2.51 Hz, 1H), 4.59 (s, 2H), 3.95 (dd, *J* = 9.16, 3.61 Hz, 1H), 3.77 (dd, *J* = 9.16, 6.92 Hz, 1H), 3.18 (dd, *J* = 11.72, 3.93 Hz, 1H), 3.15 (t, *J* = 10.06 Hz, 1H), 2.96 (t, *J* = 10.49 Hz, 1H), 2.59-2.47 (m, 2H), 2.43 (ddd, *J* = 16.14, 4.96, 2.62 Hz, 1H), 2.17 (s, 3H), 2.17-1.97 (m, 4H), 1.57-1.38 (m, 4H), 1.45 (s, 3H). **^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm** 212.84, 208.86, 172.83, 121.82, 143.01, 138.03, 128.47, 127.81, 127.77, 127.57, 73.36, 70.33, 52.67, 50.17, 46.38, 42.51, 40.91, 37.45, 36.86, 36.71, 31.62, 28.22, 24.07, 22.69, 22.50, 22.43, 21.86, 14.16. **HRMS** calculated mass for M-Bn($C_{25}H_{26}NO_4$) = 359.1495, found mass M = 359.1519. **Fp** = 140-142°C.



Tetracycle (4.67v2) (Guillaume Revol post-Doctorate work)

Tetracycle (**4.67v2**) was synthesized according to the **general procedure K** employing silyl enol ether (**4.65v)** (100 mg, 0.23 mmol), 3-buten-2-one (191 µL, 2.30 mmol), [$AuMe_4tBuXphos,SbF_6$], acetone (1 mL) and methanol (0.1 mL) as solvent to gives expected product (**4.67v2**) as a mixture of two diastereoisomers (42 mg, 43%, d.r. = 3.6:1), other isomers are observe in the crude NMR but couldn’t be isolated cleanly.

Major Diastereoisomer (4.67v2)

IR (neat, cm^{-1}) ν max 2933.3, 2866.8, 1704.7, 1446.4, 1352.5, 738.2 **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40-7.27 (m, 5H), 4.95 (dd, *J* = 4.88, 1.73 Hz, 1H), 4.57 (d, *J* = 12.14 Hz, 1H), 4.48 (d, *J* = 12.29 Hz, 1H), 3.42 (dd, *J* = 9.09, 4.82 Hz, 1H), 3.35 (dd, *J* = 9.00, 8.45 Hz, 1H), 2.94 (dt, *J* = 12.00, 3.31 Hz, 1H), 2.69-2.54 (m, 2H), 2.53-2.46 (m, 1H), 2.50-2.42 (m, 1H), 2.37 (ddd, *J* = 13.86, 4.00, 2.91 Hz, 1H), 2.18-2.12 (m, 1H), 2.16 (s, 3H), 2.10 (s, 3H), 2.06-1.98 (m, 2H), 1.99-1.91 (m, 1H), 1.90-1.82 (m, 1H), 1.76-1.65 (m, 1H), 1.66-1.57 (m, 1H), 1.49 (ddd, *J* = 18.40, 10.61, 4.53 Hz, 1H), 1.35 (s, 3H), 1.19 (q, *J* = -1.#J Hz, 1H): **^{13}C NMR (400 MHz, $CDCl_3$)** δ 212.28, 211.45, 210.88, 141.51, 138.25, 128.46, 127.72, 127.51, 123.40, 72.97, 72.31, 55.59, 51.23, 50.54, 45.51, 38.65, 34.92, 29.44, 29.24, 28.32, 26.89, 26.12, 23.78, 22.69: **HRMS** calculated mass for M-Bn $[C_{19}H_{25}O_4]$ = 331.1915, found mass M = 331.1985.

Minor Diastereoisomer (4.67v2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H), 4.89 (dd, *J* = 3.12, 2.17 Hz, 1H), 4.53-4.45 (m, 2H), 3.50-3.38 (m, 1H), 3.39-3.30 (m, 1H), 2.96 (td, *J* = 11.86, 4.19 Hz, 1H), 2.79-2.71 (m, 2H), 2.34-2.24 (m, 1H), 2.14 (s, 3H), 2.10 (s, 3H), 1.29 (s, 3H). **^{13}C NMR (400 MHz, $CDCl_3$)** δ 212.54, 211.13, 210.65, 141.68, 138.23, 128.47, 127.72, 127.57, 123.50, 73.13, 72.62, 55.65, 50.21, 46.81, 45.92, 38.83, 37.34, 31.05, 30.36, 29.72, 29.06, 28.75, 28.33, 24.46, 22.09.

7.10 Detailed Experimental: Mechanistic divergent synthesis of tricyclic core via a formal [3+2] or [4+2] cycloaadition

General Procedure L and M: Diels-Alder/ Gold(I)-Catalyzed Carbocyclization Sequence :

General Precaution

Be careful to don't have trace of silver salt in gold(I) catalyst, if not hydrolysis of silylenol ether will happen.. Be carefull to do not extend the heating time further than 24 hrs for the first Diels-Alder reaction or isomerisation of the silylenol ether can happen. In some case the diastereoselectivity of the

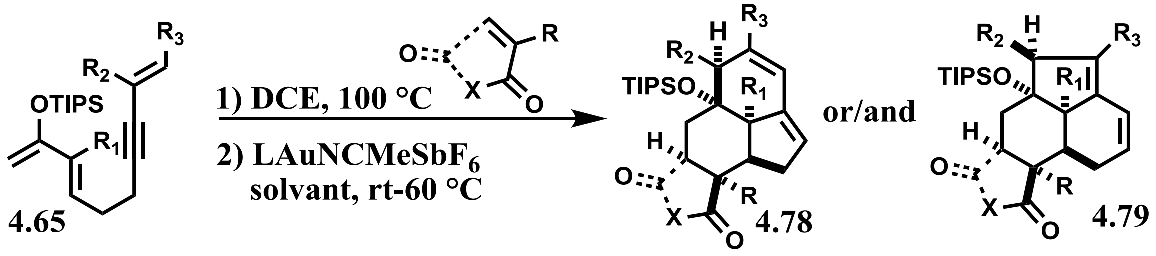
Diels-Alder reaction can be improved with longer reaction time. If phenyl maleimide is used in the first Diels-Alder, the reaction was performed at rt for 18hr instead of 100°C for 18 hr.

General Procedure L

In a sealed tube, the dienophile (1.5-5 eq.) was added to a solution of the diene (1 eq.) in DCE (10 mL/mmol). The tube was heated at 100°C for 18 hrs, then cooled down too room temperature. Gold catalyst ([Au(Me$_4$XPhos),SbF$_6$] or [Au(JohnPhos),SbF$_6$]) (5mol%) was added to the solution and the reaction was then heated to 60°C for 18hr to 48hrs. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (100:00 to 90:10)) to give the expected products.

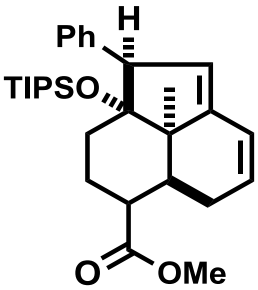
General Procedure M

In a sealed tube, the dienophile (1.5-5 eq.) was added to a solution of the diene (1 eq.) in DCE (0.1% H$_2$O) or MeNO$_2$ (10 mL/mmol). The tube was stirred at rt. for 18 hrs. Gold catalyst ([Au(NHC), BF$_4$] or [Au(JohnPhos), SbF$_6$]) (5mol%) was added to the solution and the reaction was then heated to 60°C for 18hr to 48hrs. The solvent was evaporated off under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluted with hexane/AcOEt (100:00 to 90:10)) to give the expected products.



Scheme 7.13 *Mechanistic divergent synthesis of tricyclic core via a formal [3+2] or [4+2] cycloaadition*

Formal [3+2] cycloaddition



Tricyclo[3,3,2]undecadiene (4.79s) (Guillaume Revol post-Doctorate work)

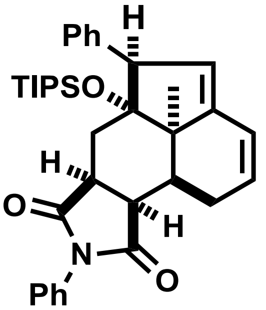
Tricyclo[3,3,2]undecadiene (**4.79s)** was synthesized according to the **general procedure L** employing silyl enol ether (**4.65s)** (100 mg, 0.25 mmol), methylacrylate (104 µL, 1.25 mmol) and [AuMe$_4$tBuXPhos, SbF$_6$] (12 mg, 0.015 mmol) in DCE (1 mL), in this particular case, the reaction wasn't heat after adding the catalyst. Crude NMR shows a 8.2:1 ratio of 6-endo:5-exo. Chromatography on silica gel afforded 114 mg (94%) of the desired product (**4.79s)** as two diastereoisomer in a 1.3:1 ratio.

Major Diastereoisomer

IR (neat, cm^{-1}) ν max 3027, 2941, 2870, 1587, 1458, 1289, 1016, 879, 683; **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ 7.37-7.16 (m, 5H), 6.21 (dd, *J* = 9.80, 2.68 Hz, 1H), 5.77-5.67 (m, 1H), 5.45 (s, 1H), 4.23 (s, 1H), 3.67 (s, 3H), 2.79-2.37 (m, 2H), 2.29 (dt, *J* = 11.99, 3.21 Hz, 1H), 2.19-2.05 (m, 1H), 1.95-1.80 (m, 1H), 1.76-1.61 (m, 2H), 1.61-1.50 (m, 1H), 1.28 (s, 3H), 1.04-0.99 (m, 21H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 175.44, 143.74, 139.58, 130.52, 127.65, 127.27, 126.64, 124.93, 87.42, 59.57, 51.37, 49.71, 41.49, 36.76, 27.72, 27.27, 22.75, 21.07, 18.65, 17.69, 14.09. **HRMS** of the mixture, calculated mass for [$C_{30}H_{44}O_3Si$] = 480.3060, found mass = 480.3083.

Minor Diastereoisomer

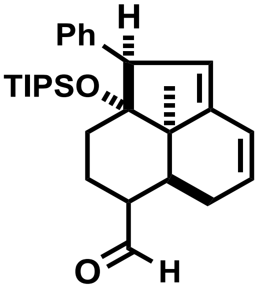
^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.37-7.16 (m, 5H), 6.12 (dd, *J* = 9.81, 2.63 Hz, 1H), 5.67-5.59 (m, 1H), 5.39 (s, 1H), 4.23 (s, 1H), 3.57 (s, 3H), 2.93 (ddd, *J* = 14.84, 10.15, 7.76 Hz, 1H), 2.79-2.37 (m, 1H), 2.29 (dt, *J* = 11.99, 3.21 Hz, 1H), 2.19-2.05 (m, 1H), 1.95-1.80 (m, 2H), 1.76-1.61 (m, 1H), 1.61-1.50 (m, 1H), 1.27 (s, 3H), 1.04-0.99 (m, 21H). **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ ppm 176.55, 144.14, 139.17, 130.21, 127.75, 126.90, 126.78, 125.83, 123.02, 87.50, 58.90, 51.51, 50.51, 45.40, 37.29, 31.50, 27.61, 24.90, 19.60, 18.70, 18.20, 14.07.



Tricyclo[3,3,2]undecadiene (4.79s2) (Guillaume Revol post-Doctorate work)

Tricyclo[3,3,2]undecadiene (**4.79s2)** was synthesized according to the **general procedure L** employing silyl enol ether (**4.65s)** (50 mg, 0.13 mmol), *N*-phenylmaleimide (33 mg, 0.19 mmol) and [AuMe$_4$tBuXPhos, SbF$_6$] (6 mg, 0.007 mmol) and DCE (1 mL) as solvent to gives 60 mg (97%) of the desired product (**4.79s2)** in mixture with 16% of formal [4+2] product.

IR (neat, cm^{-1}) ν max 2945, 2866, 1775, 1712, 1379, 883; **^{1}H NMR (400 MHz, *CDCl$_3$*)** *δ* 7.54-7.41 (m, 2H), 7.42-7.33 (m, 1H), 7.32-7.21 (m, 7H), 6.22 (d, *J* = 9.57 Hz, 1H), 6.03-5.94 (m, 1H), 5.37 (d, *J* = 1.33 Hz, 1H), 4.30 (s, 1H), 3.23 (t, *J* = 7.92 Hz, 1H), 3.16-3.07 (m, 1H), 2.58 (m, 2H), 2.36 (dd, *J* = 13.72, 5.62 Hz, 1H), 2.05 (dd, *J* = 14.33, 12.01 Hz, 1H), 1.74 (dd, *J* = 14.30, 5.52 Hz, 1H), 1.35 (s, 3H), 1.05 (s, 15H), 1.02 (s, 3H), 1.07-0.99 (m, 3H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** *δ* 178.64, 175.93, 143.77, 138.47, 131.88, 130.37, 130.33, 129.02, 128.27, 128.13, 127.23, 126.28, 124.90, 122.59, 87.42, 59.40, 49.95, 41.83, 38.46, 35.38, 31.38, 26.19, 21.88, 18.70, 17.69, 14.26.: **HRMS** calculated mass for [$C_{36}H_{45}NO_3Si$] = 567.3169, found mass = 567.3203 ; [$(M-C_3H_7)^+$] = 524.2621 found mass = 524.2669.



Tricyclo[3,3,2]undecadiene (4.79s3) (Guillaume Revol post-Doctorate work)

Tricyclo[3,3,2]undecadiene (**4.79s3)** was synthesized according to the **general procedure L** employing silyl enol ether (**4.65s)** (100 mg, 0.25 mmol), acroleine (84 μL, 1.25 mmol) and

[AuMe$_4$tBuXPhos, SbF$_6$] (12 mg, 0.015 mmol) and DCE (1 mL) as solvent to gives 90 mg (79%) of the desired product (**4.79s3**) as two diastereoisomer in a 2.5:1 ratio and 16% of formal [4+2] product.

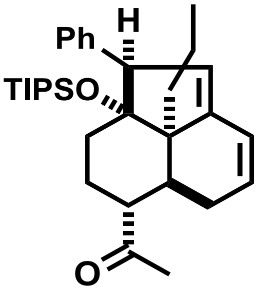
Major Diastereoisomer (4.79s)

IR (neat, cm^{-1}) ν max 2945, 2866, 1716, 1462, 882, 738, 667; **^{1}H NMR (400 MHz, *CDCl$_3$*)** *δ* 9.82 (d, *J* = 2.19 Hz, 1H), 7.33-7.19 (m, 5H), 6.22 (dd, *J* = 9.86, 2.49 Hz, 1H), 5.87-5.74 (m, 1H), 5.45 (s, 1H), 4.23 (s, 1H), 2.92-2.71 (m, 1H), 2.38-2.26 (m, 3H), 2.17 (td, *J* = 14.57, 3.24 Hz, 1H), 1.80 (dd, *J* = 13.79, 2.51 Hz, 1H), 1.60-1.53 (m, 2H), 1.30 (s, 3H), 1.03 (s, 12H), 0.99 (s, 7H), 1.09-1.04 (m, 3H). **^{13}C NMR (400 MHz, *CDCl$_3$*)** *δ* 205.84, 143.57, 138.98, 131.47, 130.32, 128.56, 127.80, 126.86, 126.70, 124.36, 87.79, 59.44, 52.20, 50.05, 38.08, 28.32, 28.21, 20.60, 20.39, 18.69, 18.65, 14.11. **HRMS** of the mixture, calculated mass for [$C_{29}H_{42}O_2Si$] = 450.2954, found mass = 450.2941; [$(M-C_3H_7)^+$] = 407.2406 found mass = 407.2429.

Minor Diastereoisomer (4.79s)

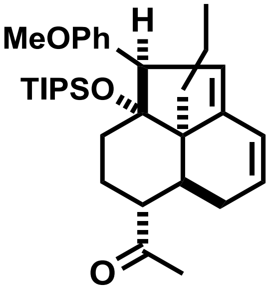
^{1}H NMR (400 MHz, *CDCl$_3$*) *δ* ppm 9.52 (d, *J* = 3.64 Hz, 1H), 7.41-7.14 (m, 5H), 6.27-6.17 (m, 1H), 5.73-5.64 (m, 1H), 5.47 (s, 1H), 4.25 (s, 1H), 1.33 (s, 3H), 1.02 (s, 12H), 0.97 (s, 6H)

^{13}C NMR (400 MHz, *CDCl$_3$*) *δ* ppm 203.93, 144.07, 139.00, 130.25, 128.51, 127.89, 126.89, 126.47, 126.11, 123.27, 87.49, 58.89, 51.31, 47.38, 44.92, 30.84, 27.04, 18.96, 18.67, 18.62, 17.77, 14.09.



Tricyclo[3,3,2]undecadiene (4.79j)

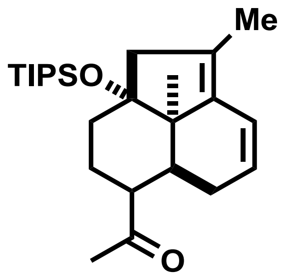
Tricyclo[3,3,2]undecadiene (**4.79j)** was synthesized according to the **general procedure L** employing silyl enol ether (**4.65j)** (100 mg, 0.236 mmol), 3-but-2-enone (45 μL, 0.49 mmol) and [[AuMe$_4$tBuXPhos, SbF$_6$] (15 mg, 0.016 mmol) and DCE (2 mL) as solvent to gives 74 mg (66%) of the desired product (**4.79j)** as a 6 : 1 ratio with the formal [4+2] product and as a sole diastereoisomer. **IR (neat, cm^{-1})** ν max 2944, 2866, 1719, 1462, 878, 738; **^{1}H-NMR (400 MHz; CDCl$_3$):** δ 7.30-7.21 (m, 5H), 6.23 (dd, J = 9.8 Hz, 2.5 Hz, 1H), 5.66 (ddd, J = 7.5 Hz, 5.7 Hz, 2.2 Hz, 1H), 5.52 (s, 1H), 4.19 (s, 1H), 2.55-2.41 (m, 2H), 2.24-2.12 (m, 2H), 2.11 (s, 3H), 1.95-1.88 (m, 1H), 1.79 (dd, J = 19.2 Hz, 6.0 Hz, 1H), 1.53-1.39 (m, 6H), 1.15 (dt, J = 14.5 Hz, 3.1 Hz, 1H), 1.04-0.96 (m, 2H), 0.89 (t, J = 6.9 Hz, 3H). **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 212.5, 142.8,139.5, 130.4, 127.9,, 127.3, 127.3, 126.9, 89.1, 59.9, 53.6, 53.5, 36.8 , 36.6, 33.2, 29.2, 28.3, 24.8, 19.6, 18.8, 15.3, 14.2: **HRMS (EI)** m/z calcd for $C_{32}H_{48}O_2Si$ 492,3424, found mass = 492.3408.



Tricyclo[3,3,2]undecadiene (4.79m)

Tricyclo[3,3,2]undecadiene (**4.79m)** was synthesized according to the **general procedure L** employing silyl enol ether (**4.65m)** (100 mg, 0.234 mmol), 3-but-2-enone (45 µL, 0.49 mmol) and [AuMe$_4$tBuXPhos, SbF$_6$] (15 mg, 0.016 mmol) and DCE (2 mL) as solvent to gives 69 mg (61%) of the desired product (**4.79m)** as a 9 : 1 ratio with the formal [4+2] product and as a sole diastereoisomer.

IR (neat, cm^{-1}) ν max 2946, 2878, 1722, 1465, 881, 739; **^{1}H-NMR (400 MHz; CDCl$_3$):** δ 7.14 (d, J =8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 6.21 (dd, J = 9.8 Hz, 2.6 Hz, 1H), 5.65 (t, J = 5.9 Hz, 1H), 5.46 (s, 1H), 4.14 (br, 1H), 3.79 (s, 3H), 2.53-2.39 (m, 2H), 2.21 (dd, J = 11.7 Hz, 5.7 Hz, 1H), 2.14-2.10 (m, 1H), 2.11 (s, 3H), 1.92-1.84 (m, 1H), 1.78 (dd, J = 19.3 Hz, 5.8 Hz, 1H), 1.52-1.40 (m, 5H), 1.17 (dt, J = 14.5 Hz, 3.0 Hz, 1H), 1.06-1.98 (m, 21H), 0.89 (t, J = 7.1 Hz, 3H) **^{13}C NMR (400 MHz, *CDCl$_3$*)** 212.6, 158.8, 142.6, 131.4, 131.3, 127.6, 127.2, 124.3, 113.3, 89.0, 58.8, 55.4, 53.5, 53.5, 36.7, 36.6, 33.1, 29.1, 28.3, 19.5, 18.8, 14.1, 12.4: **HRMS (EI)** m/z calcd for $C_{33}H_{50}O_3Si$ 522.3529, found mass = 522.3515



Tricyclo[3,3,2]undecadiene (4.79w) (Guillaume Revol post-Doctorate work)

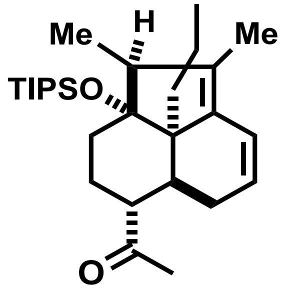
Tricyclo[3,3,2]undecadiene (**4.79w)** was synthesized according to the **general procedure L** employing silyl enol ether (**4.65b)** (50 mg, 0.15 mmol), 3-buten-2-one (61 μL, 0.75 mmol), [AuMe$_4$tBuXPhos, SbF$_6$] (7 mg, 0.008 mmol) and DCE 0.1% H$_2$O (1 mL) as solvent to gives 41 mg (71%) of a mixture of the desired product (**4.79w)** (51%) with 28% of formal [4+2] product ***9b*** (20%).

Major Diastereoisomer (4.79w)

IR (neat, cm^{-1}) ν max of the mixture, 2949, 2874, 1708, 1696, 1466, 883, 679; **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ 6.25 (dd, *J* = 9.94, 2.55 Hz, 1H), 5.56 (m, 1H), 2.73 (d, *J* = 15.03 Hz, 1H), 2.47 (d, *J* = 17.08 Hz, 1H), 2.32 (dt, *J* = 11.67, 3.18 Hz, 1H), 2.09 (s, 3H), 1.99 (dd, *J* = 11.50, 6.16 Hz, 1H), 1.68 (s, 3H), 1.63-1.54 (m, 2H), 1.09 (m, 21H), 1.04 (s, 3H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 212.83, 136.14, 129.92, 124.49, 120.64, 81.04, 52.70, 50.06, 50.03, 36.67, 36.53, 28.90, 27.22, 24.85, 20.59, 18.50, 18.43, 14.11, 13.49. **HRMS** of the mixture, calculated mass for [C$_{25}$H$_{42}$O$_2$Si] = 402.2954, found mass = 402.2937; [(M-C$_3$H$_7$)$^+$] = 359.2406 found mass =359.2394.

Minor Diastereoisomer (4.79w)

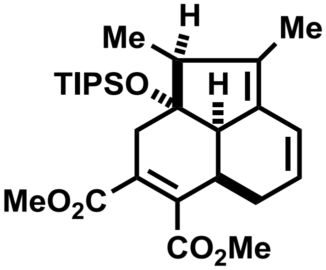
^{1}H NMR (400 MHz, *CDCl$_3$*) δ 6.19 (dd, *J* = 9.99, 1.59 Hz, 1H), 5.63-5.52 (m, 1H), 2.79-2.68 (m, 2H), 2.57-2.47 (m, 1H), 2.47-2.36 (m, 1H), 2.22 (dd, *J* = 18.71, 5.26 Hz, 1H), 2.12 (s, 3H), 2.09-2.05 (m, 1H), 1.66 (s, 3H), 1.64-1.54 (m, 2H), 1.13-1.07 (m, 21H), 1.04 (s, 3H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 212.45, 136.10, 129.19, 125.35, 122.54, 81.14, 50.68, 49.86, 38.06, 32.55, 32.28, 27.53, 22.39, 18.52, 14.05, 13.52.



Tricyclo[3,3,2]undecadiene (4.79h)

Tricyclo[3,3,2]undecadiene (**4.79h)** was synthesized according to the **general procedure L** employing silyl enol ether (**4.65h)** (100 mg, 0.350 mmol), 3-but-2-enone (68 μL, 0.84 mmol) and [AuJohnPhos, SbF_6] (12 mg, 0.016 mmol) and DCE (2 mL) as solvent to gives 92 mg (74%) of the desired product (**4.79h)** as a 7 : 1 ratio with the formal [4+2] product and as a sole diastereoisomer.

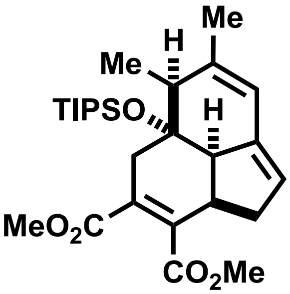
IR (neat, cm^{-1}) ν max 2940, 2876, 1715, 1458, 882; **^{1}H-NMR (400 MHz; $CDCl_3$):** δ 6.11 (dd, J = 9.9 Hz, 2.5 Hz, 1H), 5.54 (t, J = 7.3 Hz, 1H), 2.91 (dd, J = 6.4 Hz, 6.4 Hz, 1H), 2.43-2.28 (m, 2H), 2.34 (dd, J = 11.4 Hz, 5.4 Hz, 1H), 2.13-2.10 (m, 1H), 2.09 (s, 3H), 1.76-1.64 (m, 2H), 1.61 (s, 3H), 1.58-1.51 (m, 6H), 1.45-1.37 (m, 2H), 1.15-1.07 (m, 21H), 0.99 (d, J = 6.8 Hz, 1H), 0.81 (t, J = 7.2 Hz, 3H) **^{13}C NMR (101 MHz; $CDCl_3$):** δ 213.1, 134.9, 133.3, 124.9, 121.5, 85.8, 53.3, 52.2, 49.7, 36.5, 35.5, 32.4, 29.9, 29.0, 27.9, 25.0, 19.1, 18.8, 14.2, 11.4, 10.9: **HRMS (EI)** m/z calcd for $C_{28}H_{48}O_2Si$ = 444. 3424, found mass = 444.3431.



Tricyclo[3,3,2]undecadiene (4.79t) (Guillaume Revol post-Doctorate work)

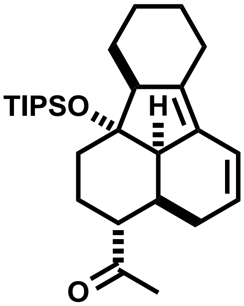
Tricyclo[3,3,2]undecadiene (**4.79t)** was synthesized according to the **general procedure L** employing silyl enol ether (**4.65t)** (100 mg, 0.30 mmol), dimethylacetylenecarboxylate (50 μL, 0.45 mmol) and [AuJohnPhos, SbF_6] (12 mg, 0.015 mmol) in DCE 0.1% H_2O (1 mL) in this particular case, the reaction wasn't heat after adding the catalyst. Crude NMR shows a 3:1 ratio of 6-endo:5-exo. Chromatography on silica gel afforded 49 mg (65%) of the desired product ***8e*** in mixture with the formal [4+2] product (**4.79u)** in a 3:1 ratio.

IR (neat, cm^{-1}) ν max 2952.9, 2874.6, 1736.0, 1454.3, 1430.8, 1266.4, 879.1, 742.1. **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ 6.28 (dd, *J* = 9.87, 2.74 Hz, 1H), 5.60-5.49 (m, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.11 (ttd, *J* = 8.27, 4.07, 1.97 Hz, 1H), 2.94-2.86 (m, 1H), 2.83-2.72 (m, 1H), 2.64 (dd, *J* = 18.20, 3.94 Hz, 1H), 2.47-2.41 (m, 1H), 2.28 (d, *J* = 6.15 Hz, 1H), 2.14 (dd, *J* = 18.14, 2.10 Hz, 1H), 1.62 (s, 3H), 1.10 (d, *J* = 7.29 Hz, 3H), 1.04 (m, 21H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ ppm 169.76, 166.89, 143.44, 134.45, 130.30, 129.48, 124.42, 121.87, 81.90, 53.27, 52.00, 51.89, 50.16, 32.17, 31.20, 27.78, 18.47, 18.29, 17.67, 14.14, 13.57, 12.26, 11.53. **HRMS** of the mixture, calculated mass for [$C_{27}H_{42}O_5Si$-[$(M-C_3H_7)^+$]] = 431.2254, found mass = 431.2257.



Tricyclo[3,2,3]undecadiene (4.78t) (Guillaume Revol post-Doctorate work)

^{1}H NMR (400 MHz, *CDCl$_3$*) δ 5.97 (s, 1H), 5.26 (s, 1H), 3.74 (s, 1H), 3.69 (s, 1H), 3.37 (t, *J* = 8.69 Hz, 1H), 3.07-2.93 (m, 1H), 2.60-2.46 (m, 1H), 2.23 (d, *J* = 6.36 Hz, 1H), 2.22-2.19 (m, 1H), 2.16 (dd, *J* = 17.20, 3.29 Hz, 1H), 1.76 (s, 1H), 1.08 (d, *J* = 7.24 Hz, 1H), 1.04 (s, 1H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 169.20, 128.55, 140.97, 140.56, 136.18, 133.40, 120.68, 119.51, 74.67, 52.27, 51.97, 51.91, 45.93, 38.14, 37.16, 21.47, 18.53, 18.34, 17.84, 15.24, 14.28, 13.91, 12.59, 11.65.

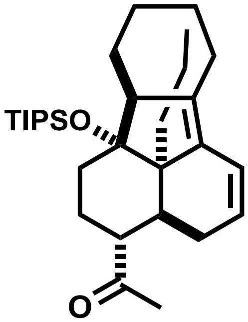


Tricyclo[3,3,2]undecadiene (4.79p)

Tricyclo[3,3,2]undecadiene (**4.79p)** was synthesized according to the **general procedure L** employing silyl enol ether (**4.65p)** (100 mg, 0.320 mmol), 3-but-2-enone (78 μL, 0.96 mmol) and

[AuMe$_4$tBuXPhos, SbF$_6$] (15 mg, 0.016 mmol) and DCE (2 mL) as solvent to gives 76 mg (67%) of the desired product (**4.79p).**

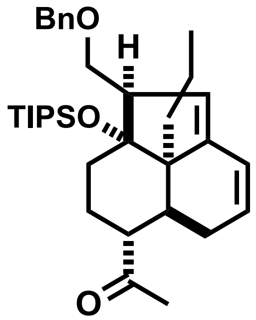
IR (neat, cm^{-1}) ν max 2951, 2868, 1712, 1462, 1133, 886; **^{1}H-NMR (400 MHz; CDCl$_3$)**: δ 6.24 (dd, *J* = 9.8, 2.7 Hz, 1H), 5.55 (dd, *J* = 7.7 Hz, 5.6 Hz, 1H), 2.77 (br, 1H), 2.62-2.53 (m, 2H), 2.39-2.34 (m, 2H), 2.30-2.22 (m, 1H), 2.09 (s, 3H), 1.91 (dd, *J* = 18.4, 6.1 Hz, 1H), 1.81-1.72 (m, 3H), 1.63-1.54 (m, 3H), 1.31-1.19 (m, 2H), 1.10-1.03 (m, 24H). **^{13}C NMR (101 MHz; CDCl$_3$):** δ 212.9, 134.8, 128.3, 125.2, 121.4, 82.7, 54.6, 52.0, 51.3, 32.1, 30.3, 29.9, 29.1, 25.4, 25.4, 25.1, 25.0, 23.8, 18.6, 13.7. **HRMS (EI)** m/z calcd for $C_{27}H_{44}O_2Si$ 428.3111, found mass = 428.3119.



Tricyclo[3,3,2]undecadiene (4.79l)

Tricyclo[3,3,2]undecadiene (**4.79l)** was synthesized according to the **general procedure L** employing silyl enol ether (**4.65l)** 100 mg, 0.317 mmol), 3-but-2-enone (78 μL, 0.96 mmol) and [AuMe$_4$tBuXPhos, SbF$_6$] (15 mg, 0.016 mmol) and DCE (2 mL) as solvent to gives 87 mg (72%) of the desired product (**4.79l).**

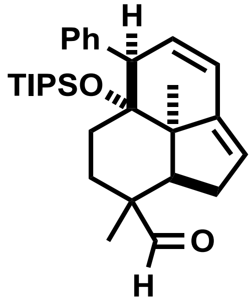
IR (neat, cm^{-1}) ν max 2966, 2855, 1709, 147, 1138, 876 ; **^{1}H-NMR (400 MHz; CDCl$_3$)**: δ δ 6.24 (dd, *J* = 9.9, 2.5 Hz, 1H), 5.53 (dd, *J* = 7.5 Hz, 4.7 Hz, 1H), 2.76-2.70 (m, 1H), 2.63 (dd, J = 15.4 Hz, 3.0 Hz, 1H), 2.42-2.31 (m, 2H), 2.21 (dd, J = 11.5 Hz, 5.9 Hz, 1H), 2.10 (s, 3H), 1.91-1.77 (m, 6H), 1.69-1.51 (m, 6H), 1.48-1.38 (m, 2H), 1.33-1.21 (m, 5H), 1.10 (d, J = 7.4 Hz, 18H), 0.80 (t, J = 7.2 Hz, 3H). **^{13}C NMR (101 MHz; CDCl$_3$):** δ δ 213.0, 134.4, 133.2, 124.8, 121.1, 85.2, 53.2, 52.7, 52.4, 36.7, 35.1, 33.9, 29.1, 28.1, 25.3, 25.2, 25.2, 25.1, 24.9, 18.9, 15.2, 14.1:. **HRMS (EI)** m/z calcd for $C_{30}H_{50}O_2Si$ 470.3580, found mass = 470.3579.



Tricyclo[3,3,2]undecadiene (4.79k)

IR (neat, cm^{-1}) ν max 2936, 2857, 1778, 1708, 1504, 1386, 1192, 746; **^{1}H-NMR (400 MHz; CDCl$_3$):** δ 7.30-7.26 (m, 5H) 6.15 (dd, J =9.8 Hz, 2.4 Hz, 1H), 5.61 (t, J =7.2 Hz,, 1H), 5.52 (s, 1H), 4.57 (d, *J* = 12.1 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 3.70 (dd, *J* = 8.3, 3.1 Hz, 1H), 3.27 (t, *J* = 9.6 Hz, 1H), 3.13 (d, *J* = 9.6 Hz, 1H), 2.41-2.33 (m, 2H), 2.18 (dd, J = 11.5 Hz, 5.5 Hz, 1H), 2.10 (s, 3H), 1.77-1.69 (m, 3H), 1.59-1.29 (m, 6H), 1.11-0.98 (m, 21H), 0.81 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz; CDCl$_3$):** δ 212.6 ,143.0,138.4,128.5, 128.2, 127.9, 127.1, 124.6, 124.0, 86.0,73.8, 69.0, 53.2, 53.1, 53.0, 36.4, 35.4, 32.6, 28.0, 24.7, 19.0, 18.7, 17.8, 14.0, 12.4: **HRMS (EI**) m/z calcd for $C_{34}H_{52}O_3Si$ 536.3686, found 536.3683

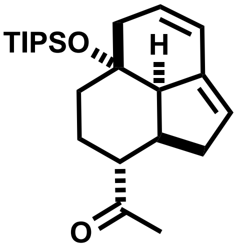
Formal [4+2] cycloaddition



Tricyclo[3,2,3]undecadiene (4.78s) (Guillaume Revol post-Doctorate work)

Tricyclo[3,2,3]undecadiene (**4.78ns)** was synthesized according to the **general procedure M** employing silyl enol ether (**4.65s)** (50 mg, 0.15 mmol), methacrolein (61 μL, 0.75 mmol), [AuMe$_4$XPhos, SbF$_6$] (7 mg, 0.008 mmol) and DCE (1 mL) as solvent to gives 41 mg (71%) of the desired product (**4.78s).**

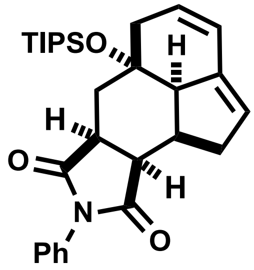
IR (neat, cm^{-1}) ν max 3050, 2945, 2870, 1747, 1724, 1466, 1254, 876; **^{1}H NMR (400 MHz, *CDCl$_3$*)** *δ* 9.45 (d, *J* = 0.68 Hz, 1H), 7.32-7.19 (m, 5H), 6.20 (dd, *J* = 9.62, 3.10 Hz, 1H), 5.57 (m, 1H), 5.46 (s, 1H), 3.98 (s, 1H), 2.71 (ddd, *J* = 16.97, 4.92, 1.58 Hz, 1H), 2.45 (dd, *J* = 17.34, 3.03 Hz, 1H), 2.21 (d, *J* = 5.23 Hz, 1H), 1.83 (dt, *J* = 13.80, 3.44 Hz, 1H), 1.73-1.38 (m, 3H), 1.28 (s, 3H), 1.02 (s, 3H), 0.99-0.90 (m, 18H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** *δ* 204.40, 149.97, 141.24, 134.98, 131.54, 127.94, 126.94, 123.47, 121.95, 79.28, 54.71, 53.85, 53.35, 45.31, 31.74, 27.34, 27.14, 24.60, 19.16, 18.98, 18.61, 15.02. **HRMS** calculated mass for [$C_{30}H_{44}O_3Si$] = 464.3110, found mass = 464.3118.



Tricyclo[3,2,3]undecadiene (4.78n1)

Tricyclo[3,2,3]undecadiene (**4.78n1)** was synthesized according to the **general procedure M** employing silyl enol ether (**4.65n)** (100 mg, 0.387 mmol), 3-but-2-enone (90 µL, 0.98 mmol) and [AuJohnPhos, SbF$_6$] (15 mg, 0.016 mmol) and DCE (1 mL) and acetone (1 mL) as solvent to gives 70 mg (62 %) of the desired product (**4.78n1)** in a diastereoisomeric ratio of 4 : 1

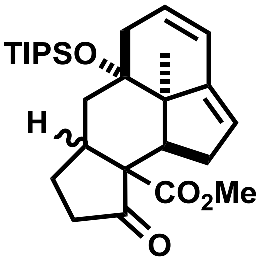
IR (neat, cm^{-1}) ν max 2945, 2866, 1716, 1462, 882, 738, 667; **^{1}H-NMR (400 MHz; CDCl$_3$):** δ 6.15 (dd, J = 9.7 Hz, 2.5 Hz, 1H), 5.58 (ddd, J = 7.8 Hz, 5.6 Hz, 2.2 Hz, 1H), 5.35 (m, 1H), 3.47 (dd, J = 12.3 Hz, 4.5 Hz, 1H), 2.67-2.59 (m, 2H), 2.50 (d, J 17.6 Hz, 1H), 2.11 (s, 3H), 2.19-2.08 (m, 1H), 1.94-1.85 (m, 1H), 1.79-1.68 (m, 1H), 1.64-1.51 (m, 4H), 1.19-1.16 (m, 3H), 1.10 (s, 18H). **^{13}C NMR (101 MHz; CDCl$_3$):** δ 211.8, 146.6, 127.7, 123.8, 122.6, 76.7, 53.8, 48.6, 43.2, 40.2, 32.9, 31.8, 28.6, 23.4, 18.6, 16.0, 13.9: **HRMS (EI)** m/z calcd for $C_{23}H_{38}O_2Si$ 374.2641, found 416.3081.



Tricyclo[3,2,3]undecadiene (4.78n2)

Tricyclo[3,2,3]undecadiene (**4.78n2)** was synthesized according to the **general procedure M** employing silyl enol ether (**4.65n)** (100 mg, 0.387 mmol), *N*-phenylmaleimide (100 mg, 0.59 mmol) and [AuJohnPhos, SbF_6] (15 mg, 0.016 mmol) and DCE (1 mL) and acetone (1 mL) as solvent to gives 79 mg (68%) of the desired product (**4.78n2).**

IR (neat, cm^{-1}) ν max 2944, 2933, 2858, 1713, 1462, 1065, 883; **^{1}H-NMR (400 MHz; $CDCl_3$):** δ 7.46-7.40 (m, 2H), 7.37-7.32 (m, 1H), 7.24-7.21 (m, 2H), 6.18 (dd, J = 9.7 Hz, 2.6 Hz, 1H), 5.63 (ddd, J = 8.3 Hz, 6.1 Hz, 2.2 Hz, 1H), 5.50 (d, J = 2.6 Hz, 1H), 3.39 (q, J = 9.5 Hz, 1H), 3.32 (t, J = 8.5 Hz, 1H), 3.28-3.22 (m, 1H), 2.98 (dt, J = 8.6 Hz, 1. 7 Hz, 1H), 2.68-2.64 (m, 3H), 2.34 (dd, J = 17.4 Hz, 5.7 Hz, 1H), 1.91 (ddd, J = 13.7 Hz, 8.3 Hz, 2.2 Hz, 1H), 1.72 (dd, J = 13.7 Hz, 10.3 Hz, 1H), 1.09 (s, 3H), 1.03 (s, 18 H). **^{13}C NMR (101 MHz; $CDCl_3$):** δ 179.8, 178.6, 140.9, 132.1, 129.2, 128.5, 127.4, 126.6, 125.6, 72.9, 53.1, 41.1, 39.7, 38.4, 35.7, 34.3, 31.2, 18.6, 13.9, 12.4: **HRMS (EI**) m/z calcd for $C_{29}H_{39}O_3NSi$ 477.2699, found mass = 477. 2691.



Tricyclo[3,2,3]undecadiene (4.78x) (Guillaume Revol post-Doctorate work)

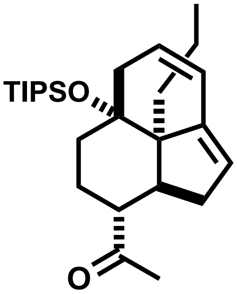
Tricyclo[3,2,3]undecadiene (**4.78x)** was synthesized according to the **general procedure M** employing silyl enol ether (**4.65b)** (100 mg, 0.31 mmol), methyl *2*-oxocyclopentadienecarboxylate (77 mg, 0.62 mmol) and [Au*i*Pr, BF_4] (10 mg, 0.015 mmol) and nitromethane (1 mL) as solvent to gives afforded 138 mg of expected product (**4.78x)** as 76 mg of one diastereoisomer (53%) and 62 mg of the other diastereoisomer (43%).

Major Diastereoisomer (4.78x)

IR (neat, cm^{-1}) ν max 2952, 2870, 1745, 1736, 1665, 1458, 124, 730; **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ 6.07 (dd, *J* = 9.57, 2.77 Hz, 1H), 5.57-5.49 (m, 1H), 5.51 (s, 1H), 3.70 (s, 3H), 3.39 (dd, *J* = 16.89, 3.29 Hz, 1H), 3.12-3.04 (m, 1H), 2.68 (d, *J* = 6.31 Hz, 1H), 2.68-2.59 (m, 1H), 2.52 (dd, *J* = 17.29, 5.87 Hz, 1H), 2.23 (m 1H), 2.18 (dd, *J* = 10.85, 8.70 Hz, 1H), 2.16-2.08 (m, 1H), 1.90 (dddd, *J* = 16.88, 12.91, 9.80, 6.22 Hz, 1H), 1.54-1.44 (m, 1H), 1.42 (d, *J* = 6.12 Hz, 1H), 1.40 (s, 1H), 1.18-1.08 (m, 21H), 1.07 (s, 3H) : **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ ppm 213.27, 172.76, 144.74, 127.17, 125.62, 122.44, 74.08, 61.08, 52.71, 52.64, 49.41, 39.03, 36.94, 36.38, 36.01, 31.36, 24.37, 19.73, 18.57, 18.50, 13.78.:**HRMS** calculated mass [(M-C_3H_7)$^+$] = 415.2305, found mass = 415.2330. **Fp** = 108-114°C.

Minor Diastereoisomer (4.78x)

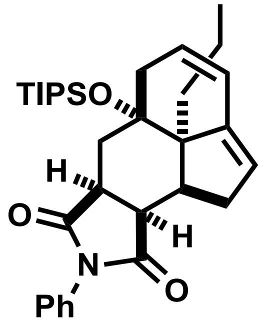
IR (neat, cm^{-1}) ν max 3050, 2945, 2870, 1747, 1724, 1466, 1254, 876; **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ 6.15 (dd, *J* = 9.58, 2.54 Hz, 1H), 5.65-5.57 (m, 1H), 5.38 (s, 1H), 3.63 (s, 3H), 2.87 (dt, *J* = 10.06, 4.22 Hz, 1H), 2.82-2.74 (m, 2H), 2.56 (d, *J* = 17.14 Hz, 1H), 2.46 (td, *J* = 18.67, 8.88 Hz, 1H), 2.29 (dd, *J* = 15.31, 10.37 Hz, 1H), 2.24-2.11 (m, 2H), 2.07 (td, *J* = 20.36, 2.91 Hz, 1H), 2.02-1.92 (m, 1H), 1.81 (dq, *J* = 8.83, 4.18 Hz, 1H), 1.35 (dd, *J* = 15.36, 4.22 Hz, 1H), 1.25 (s, 3H), 1.18-1.06 (m, 21H): **^{13}C NMR (400 MHz, *CDCl$_3$*)** δ 211.73, 170.35, 147.01, 127.26, 123.24, 123.20, 75.24, 63.46, 52.35, 52.23, 44.21, 39.62, 37.82, 35.00, 34.76, 29.68, 27.72, 20.95, 19.23, 18.84, 14.87. **HRMS** calculated mass for [(M-C_3H_7)$^+$] = 415.2305, found mass = 415.2293. **Fp** = 100-105°C.



Tricyclo[3,2,3]undecadiene (4.78g1)

Tricyclo[3,2,3]undecadiene (**4.78g1)** was synthesized according to the **general procedure M** employing silyl enol ether (**4.65g)** (100 mg, 0.375 mmol), 3-but-2-enone (90 μL, 0.98 mmol) and [AuJohnPhos, SbF_6] (15 mg, 0.016 mmol) and DCE (1 mL) and acetone (1 mL) as solvent to gives 88 mg (81%) of the desired product (**4.78g1)** in a diastereoisomeric ratio of 9 : 1

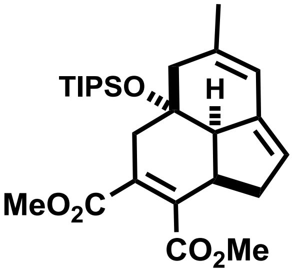
IR (neat, cm^{-1}) ν max 2941, 2866, 1716, 1458, 883; **^{1}H-NMR (400 MHz; CDCl$_3$):** δ 5.85 (dd, J = 9.7 Hz, 2.3 Hz, 1H), 5.57-5.51 (m, 1H), 5.42 (s, 1H), 3.53-3.46 (m, 1H), 2.71 (t, J 6.7 Hz, 1H), 2.71 (t, J = 6.7 Hz, 1H), 2.55 (d, J = 17.8 Hz, 1H), 2.44 (dd, J = 18.0 Hz, 8.7 Hz, 1H), 2.14-2.09 (m, 2H), 2.12 (s, 3H), 1.88 (d, J = 18.0 Hz, 1H), 1.78 (td, J = 12.8 Hz, 4.2 Hz, 1H), 1.72-1.62 (m, 2H), 1.61-1.50 (m, 3H), 1.44 (td, J = 12.8 Hz, 4.4 Hz, 1H), 1.32-1.21 (m, 3H), 1.10 (s, 18H), (t, J = 7.3 Hz, 3H). **^{13}C NMR (101 MHz; CDCl$_3$):** δ 211.9, 143.4, 127.7, 125.3, 123.8, 77.4, 57.3, 48.2, 40.7, 40.6, 37.5, 34.6, 31.8, 28.6), 18.6, 18.5, 16.4, 15.5, 15.1, 13.9: **HRMS (EI)** m/z calcd for $C_{26}H_{44}O_2Si$ [$(M-C_3H_7)^+$] 416.3111, found mass = 416.3081.



Tricyclo[3,2,3]undecadiene (4.78g2)

Tricyclo[3,2,3]undecadiene (**4.78g2)** was synthesized according to the **general procedure M** employing silyl enol ether (**4.65g)** 100 mg, 0.375 mmol), N-phenylmaleimide (100 mg, 0.59 mmol) and [AuJohnPhos, SbF$_6$] (15 mg, 0.016 mmol) and DCE (1 mL) and acetone (1 mL) as solvent to gives 99 mg (90%) of the desired product (**4.78g2).**

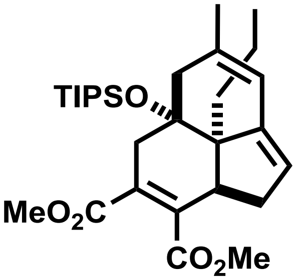
IR (neat, cm^{-1}) ν max 2946, 2936, 2865, 1713, 1458, 1063, 883; **^{1}H-NMR (400 MHz; CDCl$_3$):** δ 7.47 (t, J = 7.1 Hz, 2H), 7.38 (ddd, J = 7.5 Hz, 7.5 Hz, 1.1 Hz, 1H), 7.29 (t, J =7.2 Hz, 2H), 6.12 (dd, J = 9.9 Hz, 2.1 Hz, 1H), 5.61 (ddd, J = 9.9 Hz, 5.6 Hz, 2.1 Hz, 1H), 5.42 (s, 1H), 3.52 (t, J = 9.4 Hz, 1H), 3.30 (q, J = 10.0 Hz, 1H), 2.87 (td, J = 9.5 Hz, 4.0 Hz, 1H), 2.79-2.66 (m, 2H), 2.27 (dd, J = 18.0 Hz, 5.2 Hz, 1H), 2.01 (dt, J = 19.0 Hz, 2.9 Hz, 2.2 Hz, 1H), 1.98-1.87 (m, 2H), 1.65 (td, J= 12.8 Hz, 4.8 Hz, 1H), 1.50 (td, J = 12.7 Hz, 4.8 Hz, 1H), 1.28-0.98 (m, 2H), 1.17 (s, 18H), 1.09 (s, 3H), 0.89 (t, J = 6.8 Hz, 3H). **^{13}C NMR (101 MHz; CDCl$_3$):** δ 179.9, 179.3, 144.2, 132.1, 129.2, 128.6, 126.5, 126.4, 123.9, 123.0, 77.3, 57.7, 41.4, 39.9, 39.6, 37.7, 36.8, 36.0, 31.7, 18.9, 17.8, 17.3,12.4: **HRMS (EI)** m/z calcd for $C_{32}H_{45}O_3NSi$ 519.3169, found mass = 519.3171.



Tricyclo[3,2,3]undecadiene (4.78o)

Tricyclo[3,2,3]undecadiene (**4.78o)** was synthesized according to the **general procedure M** employing silyl enol ether (**4.65p)** (100 mg, 0.378 mmol), dimethylacetylenecarboxylate (100 μL, 090 mmol) and [AuJohnPhos, SbF_6] (15 mg, 0.016 mmol) and DCE (1 mL) as solvent to gives 71 mg (62%) of the desired product (**4.78o).**

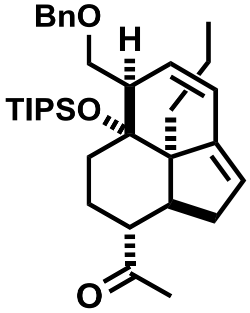
IR (neat, cm^{-1}) ν max 2952, 2874, 1736, 1454, 1430, 1266, 879, 742; **^{1}H-NMR (400 MHz; $CDCl_3$)**: δ 5.95 (s, 1H), 5.29 (d, *J* = 1.8 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.37 (td, J = 7.5 Hz, 2.8 Hz, 1H), 2.93 (m, 1H), 2.73 (dd, *J* = 17.4, 7.9 Hz, 1H), 2.51 (d, *J* = 16.9 Hz, 1H), 2.39 (dd, *J* = 17.2, 3.2 Hz, 2H), 2.23-2.16 (m, 2H), 1.79 (s, 3H), 1.11-1.04 (m, 3H), 1.04 (s, 18H). **^{13}C NMR (101 MHz; $CDCl_3$):** δ 169.2, 168.6, 141.1, 138.2, 137.5, 131.1, 121.1, 118.9, 71.2, 52.1, 51.8, 45.7, 38.1, 37.0, 34.7, 23.5, 18.4, 13.4:. **HRMS (EI)** m/z calcd for $C_{26}H_{40}O_5Si$ [$(M-C_3H_7)^+$] 417.2097, found mass = 417.2108.



Tricyclo[3,2,3]undecadiene (4.78i)

Tricyclo[3,3,2]undecadiene (**4.78i)** was synthesized according to the **general procedure M** employing silyl enol ether (**4.65i)** (100 mg, 0.376 mmol), dimethylacetylenecarboxylate (100 μL, 090 mmol) and [AuJohnPhos, SbF_6] (15 mg, 0.016 mmol) and DCE (1 mL) as solvent to gives 77 mg (71%) of the desired product (**4.78i)**.

IR (neat, cm^{-1}) ν max 2952, 2874, 1736, 1454, 1430, 1266, 879, 742; **^{1}H-NMR (400 MHz; $CDCl_3$):** δ 5.89 (s, 1H), 5.33 (s, 1H), 3.75 (s, 3H), 3.69(s, 3H), 3.00 (dd, *J* = 7.5 Hz, 1.6 Hz, 1H), 2.71 (dd, J = 17.5 Hz, 8.3 Hz, 1H), 2.63 (d, *J* = 16.9 Hz, 1H), 2.44 (dd, *J* = 17.3, 2.7 Hz, 1H), 2.32-2.24 (m, 2H), 2.07 (d, *J* = 17.5 Hz, 1H), 1.86 (td, *J* = 12.7, 3.8 Hz, 1H), 1.77 (s, 3H), 1.42-1.16 (m, *3*H), 1.12-1.01 (m, 21H), 0.87 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (101 MHz; CDCl$_3$):** δ 164.5, 168.4, 143.4, 141.2, 136.1, 128.7, 121.7, 118.7, 74.1, 55.4, 52.2, 52.0, 44.1, 43.8, 38.2, 36.7, 36.3, 23.4, 18.5, 17.3, 15.1, 13.7: **HRMS (EI**) m/z calcd for $C_{29}H_{46}O_5Si$ [$(M-C_3H_7)^+$] 459.2567, found mass = 459.2468.



Tricyclo[3,2,3]undecadiene (4.78k)

Tricyclo[3,2,3]undecadiene (**4.78k)** was synthesized according to the **general procedure M** employing silyl enol ether (**4.65k)** (100 mg, 0.366 mmol), 3-but-2-enone (90 μL, 0.98 mmol) and [AuJohnPhos, SbF$_6$] (15 mg, 0.016 mmol) and DCE (1 mL) and MeNO$_2$ (1 mL) as solvent to gives 62 mg (57 %) of the desired product (**4.78k)** as a 2.2 : 1 ratio with the formal [4+2] product ***8q***.

IR (neat, cm^{-1}) ν max 2936, 2857, 1778, 1708, 1504, 1386, 1192, 746; **^{1}H-NMR (400 MHz; CDCl$_3$):** δ 7.39-7.27 (m, 5H) 6.22 (dd, J =9.7 Hz, 2.8 Hz, 1H), 5.76 (t, J =9.9 Hz,, 1H), 5.49 (s, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 3.77 (dd, *J* = 8.0, 3.1 Hz, 1H), 3.25 (t, *J* = 8.1 Hz, 1H), 2.82 (d, *J* = 9.6 Hz, 1H), 2. 61 (dd, J = 17.1 Hz, 3.5 Hz, 1H), 2.51 (dd, J = 10.3 Hz, 5.1 Hz, 1H), 2.25-2.16 (m, 2H), 2.09 (s, 3H), 1.78-1.58 (m, 5H), 1.52-1.33 (m, 4H), 1.07-0.98 (m, 3H), 1.05 (s, 18H), 0.79 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz; CDCl$_3$):** δ 211.7, 144.7,138.3,130.5, 128.5, 128.1, 127.9, 123.9, 123.0, 78.3,73.7, 56.0, 55.8, 46.4, 43.7, 39.2, 37.2, 31.1, 29.0, 28.8, 22.4, 18.9, 14.3, 12.4: **HRMS (EI**) m/z calcd for $C_{34}H_{52}O_3Si$ = 536.3686, found mass = 536.3683

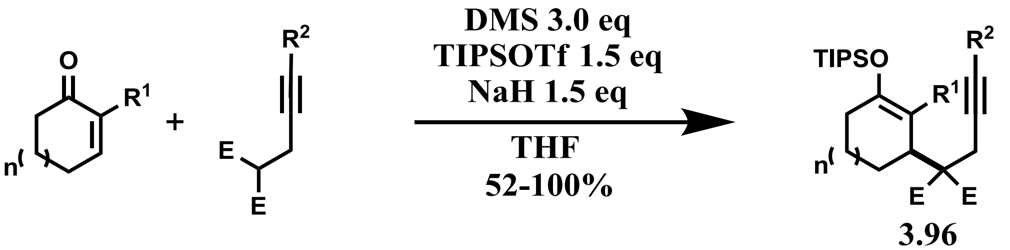
References

(1) Han, Y.; Zhu, L.; Gao, Y.; Lee, C.-S. *Org. Lett.*, **2011**, *13*, 588

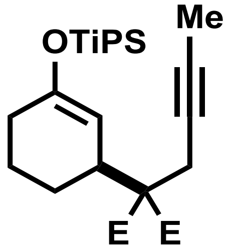
Experimental Chapter 5: *Selective divergent synthesis of fused carbocycle, silver(I) and copper(I) catalysis*

7.11 Detailed Experimental: Internal alkyne with methyl substitution and terminal alkyne

General procedure E - 1-4 addition of diethyl propargylmalonate on alkenone



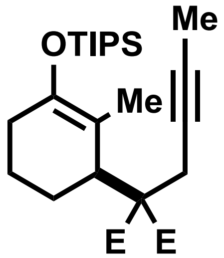
Scheme 7.14 *addition of diethyl propargylmalonate on cycloalkenone*



Silyl enol ether (5.04a)

Silyl enol ether **(5.04a)** was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as colorless oil.

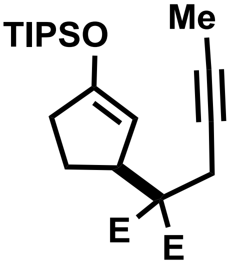
IR (neat, cm^{-1}) ν max 3056, 2943-2867, 1734, 1665, 1464, 1327, 1190; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.94-4.89 (m, 1H), 4.18 (dq, J = 15. 5 Hz, 7.1 Hz, 2H), 4.18 (dq, J = 15. 5 Hz, 7.1 Hz, 2H), 3.17-3.11 (m, 1H), 2.75 (dd, J = 5.8 Hz, 2.6 Hz, 2H), 2.13-1.90 (m, 2H), 1.87-1.78 (m, 2H), 1.72 (t, J = 2.5 Hz, 3H), 1.59-1.54 (m, 1H), 1.29-1.18 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.15-1.10 (m, 3H), 1.06 (d, J =7.1 Hz, 18H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.3 (C_{quat}), 170.2 (C_{quat}), 152.5 (C_{quat}), 104.2 (CH), 78.3 (C_{quat}), 74. 5 (C_{quat}), 61.2 (CH_2), 61.2 (CH_2), 60.8 (C_{quat}), 38.7 (CH), 29.7 (CH_2), 24.2 (CH_2), 23.0 (CH_2), 22.6 (CH_2), 18.1 (CH_3x6), 14.2 (CH_3x2), 12.7 (CH_3), 12.6 (CHx3); **HRMS (EI)** m/z calcd for $C_{26}H_{44}O_5Si$ [M^+] 464.2958 found 464.2948.



Silyl enol ether (5.04b)

Silyl enol ether **(5.04b)** was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as colorless oil.

IR (neat, cm^{-1}) ν max 3033, 2953-2887, 1734, 1655, 1486, 1311, 1097; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.21-4.11 (m, 4H), 4.23 (t, J = 5.9 Hz, 1H), 2.75 (dq, J = 16.8 Hz, 2.5 Hz, 1H), 2.71 (dq, J = 16.8 Hz, 2.5 Hz, 1H), 2.06-1.99 (m, 2H), 1.73 (t, J = 2.5 Hz, 3H), 1.71-1.65 (m, 3H), 1.63 (s, 3H), 1.55-1.46 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 1.13-1.08 (m, 3H), 1.06 (d, J =7.1 Hz, 18H) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 171.0 (C_{quat}), 170.9 (C_{quat}), 147.2 (C_{quat}), 111.2 (CH), 77.9 (C_{quat}), 75.4 (C_{quat}), 61.4 (C_{quat}), 61.2 (CH_2), 61.2 (CH_2), 42.9 (CH), 30.3 (CH_2), 25.6 (CH_2), 24.6 (CH_2), 21.2 (CH_2), 18.2 (CH_3x6), 15.5 (CH_3), 14.0 (CH_3x2), 13.7 (CH_3), 12.6 (CHx3), **HRMS (EI)** m/z calcd for $C_{27}H_{46}O_5Si$ 478.3115 found 478.3119.



Silyl enol ether (5.04c)

Silyl enol ether **(5.04c)** was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as colorless oil.

IR (neat, cm^{-1}) ν max 2952, 2834, 1733, 1472, 1325, 879; **^{1}H ^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.77(dd, J = 3.4 Hz, 1,7 Hz, 1H), 4.24-4.07 (m, 4H), 3.59-3.52 (m, 1H), 2.73 (dq, J = 16.9 Hz, 2.6 Hz, 1H), 2.69 (dq, J= 16.9 Hz, 2.6 Hz, 1H), 2.32-2.21 (m, 2H), 2.04 (dddd, J = 13.2 Hz, 8.8 Hz, 8.8 Hz, 4.5 Hz, 1H), 1.88-1.79 (m, 1H), 1.73 (dd, J = 2.6 Hz, 3H), 1.25 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.23 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.18-1.13 (m, 3H), 1.06 (d, J= 7.2 Hz, 18H) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.5 (C_{quat}x2), 156.8 (C_{quat}), 102.9 (CH), 78.2 (C_{quat}), 74.5 (C_{quat}), 61.2 (CH_2x2), 60.8 (C_{quat}), 45.5 (CH), 33.1 (CH_2), 23.7 (CH_2), 23.0 (CH_2), 18.0 (CH_3x6), 17.8 (CH_3), 14.2 (CH_3), 12.5 (CH), 12.0 (CHx3); **HRMS (EI)** m/z calcd for $C_{25}H_{42}O_5Si$ 450.2802, found 450.2790

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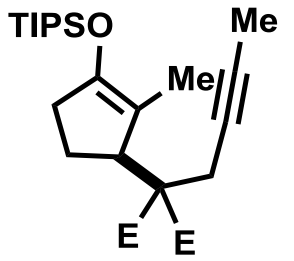
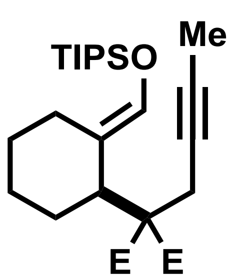


Silyl enol ether (5.04d)

Silyl enol ether **(5.04d)** was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as colorless oil.

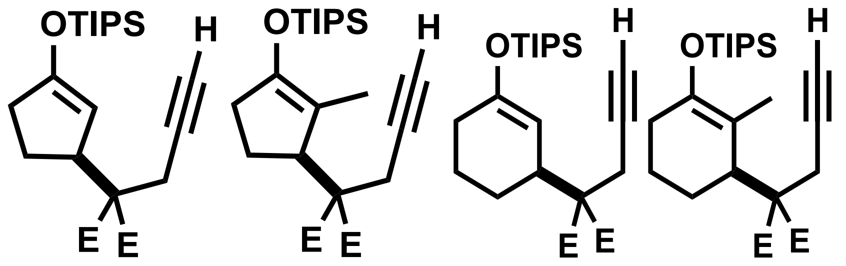
IR (neat, cm^{-1}) ν max 2944, 2867, 1734, 1465, 1225, 883; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.22-4.10 (m, 4H), 3.52-3.47 (m, 1H), 2.84 (dq, J = 17.0 Hz, 2.6 Hz, 1H), 2,68 (dq, J = 17.0 Hz, 2,6 Hz, 1H), 2.37-2.27 (m, 1H), 2.23-2.13 (m, 1H), 2.12-2.05 (m, 1H), 1.91 (dddd, J = 13.5 Hz, 9.2 Hz, 4,6 Hz, 4.6 Hz, 1H), 1.73 (dd, J = 2.6 Hz, 2.6 Hz, 3H), 1.54 (d, J = 0.9 Hz, 3H), 1.25 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.23 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.19-1.10 (m, 3H), 1.07-1.03 (m, 18H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.7 (C_{quat}), 170.5 (C_{quat}), 150.5 (C_{quat}), 112.0 (CH), 78.0 (C_{quat}), 75.0 (C_{quat}), 61.3 (CH_2), 61.2 (CH_2), 61.1 (C_{quat}), 48.9 (CH), 32.3 (CH_2), 23.7 (CH_2), 23.3 (CH_2), 18.0 (CH_3x6), 17.8 (CH_3), 14.2 (CH_3), 14.1 (CH_3), 13.0 (CHx3); **HRMS (EI)** m/z calcd for $[M^+]$ $C_{26}H_{44}O_5Si$ 464.2958, found 464.2936.



Silyl enol ether (5.X1)

Silyl enol ether **(5.X1)** was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as colorless oil.

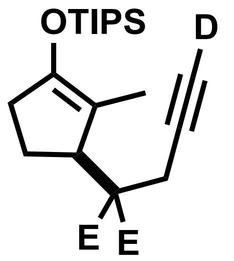
^{1}H NMR (400 MHz, CDCl$_3$) δ 6.47 (s, 1H), 4.28-4.06 (s, 4H), 3.01 (dd, J = 6.3 Hz, 3,4 Hz, 1H), 2.78 (dq, J = 16.6 Hz, 2.6 Hz, 1H), 2.72 (dq, 16.6 Hz, 2.6 Hz, 1H), 2.54 (dt, J = 13.5 Hz, 2.0 Hz, 1H), 2.14-2.07 (m, 1H), 1.80-1.72 (m, 4H), 1.71 (dd, J = 2.6 Hz, 2.6 Hz, 1H), 1.58-1.46 (m, 3H), 1.35-1.22 (m, 1H), 1.26 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.24 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.18-1.11 (m, 3H), 1.07 (d, J = 7.1 Hz, 18H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 172.1 (C$_{\text{quat}}$), 171.0 (C$_{\text{quat}}$), 136.3 (CH), 118.1 (C$_{\text{quat}}$), 78.4 (C$_{\text{quat}}$), 75.0 (C$_{\text{quat}}$), 61.4 (CH$_2$), 61.2 (CH$_2$), 59.6 (C$_{\text{quat}}$), 40.9 (CH), 29.3 (CH$_2$), 26.6 (CH$_2$), 25.5 (CH$_2$), 23.7 (CH$_2$), 22.7 (CH$_2$), 17.9 (CH$_3$x6), 17.9 (CH$_3$), 14.2 (CH$_3$), 14.0 (CH$_3$), 12.1 (CHx3)**;** **HRMS (EI)** m/z calcd for $C_{27}H_{46}O_5Si$ 478,3115, found 478.3120.



Silyl enol ethers (5.09a-d)[1]

Silyl enol ethers was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as colorless oil. Spectral data is in accordance with reported data and full characterization is available through the literature

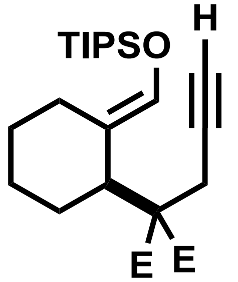
Corresponding bicycloalkenones was prepared according to **general procedure G** or **O** Gold(I) or Copper(I)-Catalyzed Carbocyclization and isolated as a colorless oil. Exhibited spectral data are in accordance with previous reported.



Silyl enol ether (5.09h)

Silyl enol ether **(5.09h)** was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as colorless oil.

IR (neat, cm^{-1}) ν max 2944, 2867, 1734, 1465, 1225, 883; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 4.25-4.11 (m, 4H), 3.55-3.50 (m, 1H), 2.84 (d, J = 17.2 Hz, 1H), 2,68 (d, J = 17.1 Hz, 1H), 2.39-2.29 (m, 1H), 2.23-2.15 (m, 1H), 2.12-2.06 (m, 1H), 1.91 (dddd, J = 13.5 Hz, 9.2 Hz, 4,6 Hz, 4.6 Hz, 1H), 1.54 (s, 3H), 1.25 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.23 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.15-1.03 (m, 21H) **^{13}C NMR (100 MHz, CDCl$_3$)** δ 170.4 (C$_{quat}$), 170.2 (C$_{quat}$), 150.8 (C$_{quat}$), 111.6 (C$_{quat}$), 80.6 (C$_{quat}$), 70.8 (C$_{quat}$), 61.5 (CH$_2$), 61.5 (CH$_2$), 60.8 (C$_{quat}$), 49.1 (CH), 32.4 (CH$_2$), 23.7 (CH$_2$), 22.7(CH$_2$), 18.0 (CH$_3$x6), 14.2 (CH$_3$), 14.1 (CH$_3$), 13.0 (CHx3) 11.8 (CH$_3$). **HRMS (EI)** m/z calcd for [M$^+$] $C_{25}H_{41}DO_5Si$ 451.2864, found 451.2862.



Silyl enol ether (5.X2)

Silyl enol ether **(5.X2)** was prepared according to the **general procedure E** 1-4 addition of diethyl propargylmalonate on cycloalkenone and isolated as colorless oil.

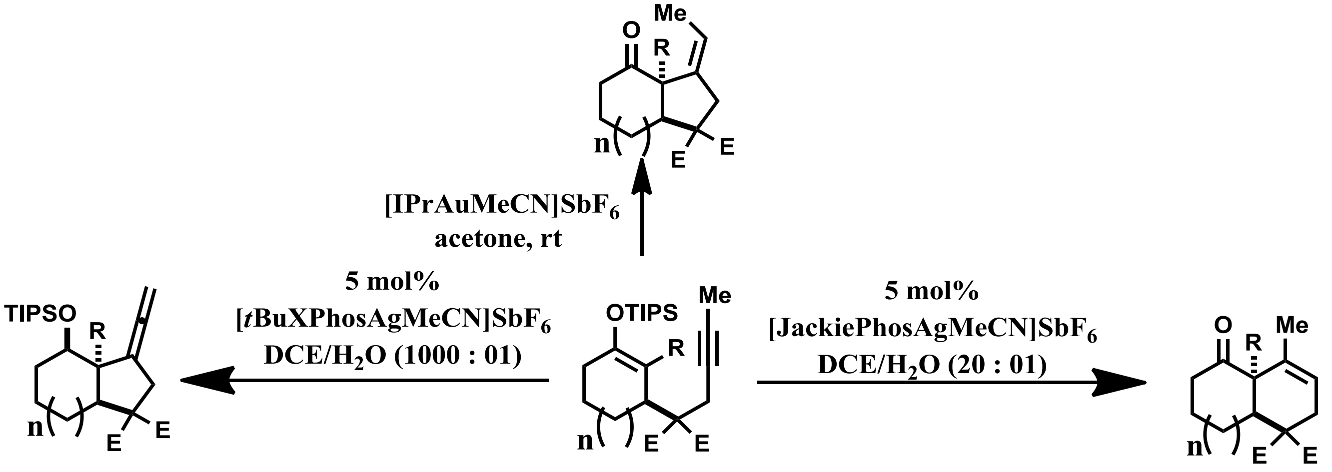
^{1}H NMR (400 MHz, CDCl$_3$) δ 6.46 (s, 1H), 4.30-4.08 (m, 4H), 3.03 (dd, J = 6.1 Hz, 3.7 Hz, 1H), 2.88 (dd, J = 16.8 Hz, 2.6 Hz, 1H), 2.80 (dd, J = 16.8 Hz, 2.7 Hz, 1H), 2.52 (dt, J = 13.7 Hz, 4.4 Hz, 1H), 2.13-2.06 (m, 1H), 1.95 (dd, J = 2.7 Hz, 2.6 Hz, 1H), 1.83-1.72 (m, 2H), 1.59-1.46 (m, 3H), 1.27 (dd, J = 7.1 Hz, 7,1 Hz, 3H), 1.25 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.19-1.10 (m, 3H), 1.07 (d, J = 7.2 Hz, 18H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.1 (C$_{quat}$), 170.6 (C$_{quat}$), 136.4 (C$_{quat}$), 118.0 (C$_{quat}$), 80.5 (C$_{quat}$), 71.3 (CH), 61.6 (CH$_2$), 61.4 (CH$_2$), 59.3 (C$_{quat}$), 41.1 (CH), 29.4 (CH$_2$), 26.6 (CH$_2$), 25.2 (CH$_2$), 23.8 (CH$_2$), 22.9 (CH$_2$), 17.9 2 (CH$_3$), 14.2 (CH$_3$), 13.9 (CH$_3$), 12.1 (CH)**; HRMS (EI)** m/z calcd for $C_{26}H_{44}O_5Si$ 464.2958, found 464.2950.

General Procedure N: Silver(I)--Catalyzed cyclizations

A reaction vessel was charged with a magnetic stirrer and purged with argon. A solution of the silyl enol ether (0.100 mmol), solvent (1.5 ml), water (75 µL) and the appropriate Ag(I) catalyst (0.010 mmol) is added via syringe. The reaction mixture is stirred at r.t. or 60°C for 1.5 days. Upon completion, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel eluted with hexane/AcOEt (9:1 to 6:1) to give the cyclization products.

N1 : solvent = DCE

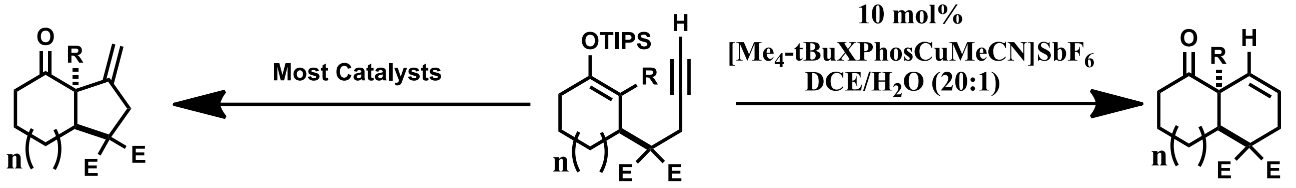
N2 : solvent = DCE: H_2O (20:1)



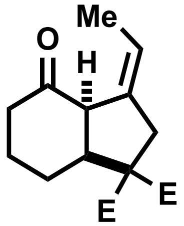
Scheme 7.15 *selective divergent silver(I)-catalyzed synthesis of fused carbocycle*

General Procedure O: Copper(I)--Catalyzed cyclization

A reaction vessel was charged with a magnetic stirrer and the appropriate Cu(I) catalyst (0.010 mmol). This vessel is then purged with argon and a solution of the silyl enol ether (0.100 mmol), solvent (1.5 ml) and water (75 µL) is added via syringe. The reaction mixture is stirred at r.t. or 60°C for 1.5 days. Upon completion, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel eluted with hexane/AcOEt (9:1 to 6:1) to give the cyclization products



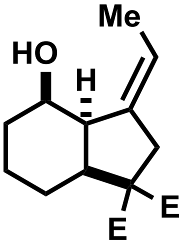
Scheme 7.16 *selective copper(I)-catalyzed 6-endo-dig cyclization with terminal alkyne*



Bicyclo[3,4,0]alkenone (5.07a)

Bicyclo[3,4,0]alkenone (**5.07a**) was prepared according to the **general procedure G** Gold-Catalyzed Carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

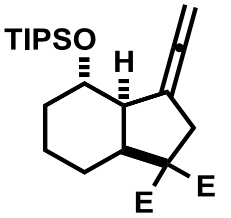
IR (neat, cm^{-1}) ν max 2980- 2941, 1733, 1725, 1240, 1178 ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.54-5.50 (m, 1H), 4.24-4.06 (m, 4H), 3.56 (br, 1H), 3.27 (ddd, J = 16.9 Hz, 2.6 Hz, 2.6 Hz, 1H), 3.18 (ddd, J = 12.4 Hz, 6.3 Hz, 6.3 Hz, 1H), 2.78 (d, J = 16.9 Hz, 1H), 2.31-2.27 (m, 2H), 2.01-1.93 (m, 1H), 1.70-1.52 (m, 2H), 1.48-1.66 (m, 3H), 1.33 (dq, J= 12.8 Hz, 3.8 Hz, 1H), 1.20 (t, J = 7.3 Hz, 3H), 1.17 (t, J = 7.3 Hz, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 211.2 (C$_{quat}$), 170.8 (C$_{quat}$), 169.3 (C$_{quat}$), 134.7 (C$_{quat}$), 122.1 (CH), 62.7 (C$_{quat}$), 61.7 (CH$_2$), 61.7 (CH$_2$), 55.6 (CH), 48.1 (CH), 39.3 (CH$_2$), 26.7 (CH$_2$), 24.5 (CH$_2$), 24.3 (CH$_2$), 14.1 (CH$_3$), 14.0 (CH$_3$), 13.8 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{17}H_{24}O_5$ 308.1624 found 308.1624.



Bicyclo[3,4,0]alkenol (5.X3)

Bicyclo[3,4,0]alkenol **(5.X1)** was prepared according to the general procedure for the reduction of ketone with $NaBH_4$ in MeOH/THF and isolated as a clear oil.

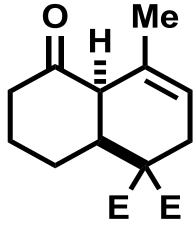
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (ddq, J = 8.0 Hz, 6.9 Hz, 2.3 Hz, 1H), 4.24-4.10 (m, 5H), 4.14 (dq, J = 18.4 Hz, 7.2 Hz, 2H), 3.15 (dddd, J = 15.6 Hz, 2.5 Hz, 2.5 Hz, 2.5 Hz, 2.5 Hz, 1H), 3.01-2.96 (m, 1H), 2.94-2.88 (m, 1H), 2.61 (dd, J= 15.6 Hz, 1.0 Hz, 1H), 1.91-1.84 (m, 2H), 1.76-1.66 (m, 2H), 1.63 (dd, J= 7.0 Hz, 1.5 Hz, 3H), 1.52-1.45 (m, 2H), 1.31-1.17 (m, 1H), 1.24 (t, J = 7.3 Hz, 3H), 1.21 (t, J = 7.3 Hz, 3H) ; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 172.0 (C_{quat}), 170.6 (C_{quat}), 139.2 (C_{quat}), 119.7 (CH), 66.2 (CH), 62.8 (C_{quat}), 61.4 (CH_2), 61.4 (CH_2), 45.7 (CH), 42.2 (CH), 41.7 (CH_2), 26.3 (CH_2), 20.6 (CH_2), 16.3 (CH_2), 14.1 (CH_3), 14.1 (CH_3), 14.0 (CH_3), ; **HRMS (EI)** m/z calcd for $C_{17}H_{26}O_5$ 310.1780, found 310.1753



Bicyclo[3.4.0]alkenol (5.06a)

Bicyclo[3,4,0]alkenol (**5.06a**) was prepared according to the **general procedure N1**Silver(I)-Catalyzed Carbocyclization at 60°C with **tBuXPhos**$AgNCMeSbF_6$ as catalyst and isolated as a clear oil.

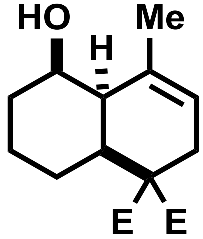
IR (neat, cm^{-1}) ν max 2988, 2944, 2891, 1739, 1452, 1312; **^{1}H NMR (300MHz, $CDCl_3$)** δ = 4.83 - 4.66 (m, 2 H), 4.28 - 4.03 (m, 5 H), 3.37 (dtd, *J* = 2.6, 5.1, 17.6 Hz, 1 H), 3.06 (q, *J* = 6.5 Hz, 1 H), 3.00 - 2.87 (m, 2 H), 1.73 (s, 2 H), 1.66 - 1.51 (m, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.06 (s, 18 H), 1.48 - 0.84 (m, 6 H); **^{13}C NMR (75MHz, $CDCl_3$)** □ = 201.3 (C_{quat}), 170.5 (C_{quat}), 160.7 (C_{quat}), 99.8 (C_{quat}), 77.4 (CH_2), 66.3 (CH), 62.0 (CH), 60.6 (CH_2), 60.5 (CH_2), 47.4 (CH), 40.5 (CH), 33.7 (CH_2), 28.2 (CH_2), 23.1 (CH_2), 17.3 (6xCH_3), 13.3 (CH_3), 13.1 (CH_3), 11.5 (3xCH); **HRMS (EI)** m/z calcd for $C_{23}H_{35}O_5Si$ [$(M-iPr)^+$] 421.2410, found 421.2427.



Bicyclo[4.4.0]alkenone (5.08a)

Bicyclo[4,4,0]alkenone (**5.08a**) was prepared according to the **general procedure N2** Silver(I)-Catalyzed Carbocyclization at 60°C with **JackiePhos**AgNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2984, 2940, 2870, 1733, 1445, 1239, 1179; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.50 (d, J = 2.7Hz, 1H), 4.22-4.10 (m, 4H), 3.25 (br, 1H), 2.88-2.83 (m, 1H), 2.80-2.73 (m, 1H), 2.62 (dddd J = 18.6 Hz, 4.2 Hz, 2.3 Hz, 2.3 Hz, 1H), 2.32-2.26 (m, 1H), 2.24-2.15 (m, 1H), 2.04-1.97 (m, 1H), 1.67-1.54 (m, 3H), 1.50 (d, J = 1.2 Hz, 3H), 1.22 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.20 (dd, J = 7.1 Hz, 7.1 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 212.0 (C$_{quat}$), 170.2 (C$_{quat}$), 169.8 (C$_{quat}$), 128.3 (C$_{quat}$), 121.0 (CH), 61.8 (CH$_2$), 61.7 (CH$_2$), 56.4 (C$_{quat}$), 54.4 (CH), 40.0 (CH), 39.8 (CH$_2$), 26.8 (CH$_2$), 25.0 (CH$_2$), 23.6 (CH$_2$), 14.1 (CH$_3$), 14.0 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{17}H_{24}O_5$ [M$^+$] 308.1624 found 308.1629.

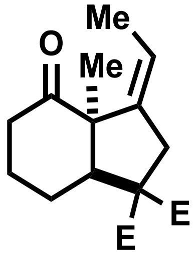


Bicyclo[4,4,0]alkenol (5.X5)

Bicyclo[4,4,0]alkenol **(5.X5)** was prepared according to the general procedure for the reduction of ketone with NaBH$_4$ in MeOH/THF and isolated as a clear oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 5.41-5.38 (m, 1H), 4.22-4.10 (m, 4H), 3.84(br, 1H), 2.77-2.71 (m, 1H), 2.70-2.66 (m, 1H), 2.52-2.44 (m, 2H), 1.83 (dd, J =2.5 Hz, 1.2 Hz, 3H), 1.77-1.69 (m, 2H), 1.56 (br, 1H), 1.43-1.32 (m, 3H), 1.25-1.19 (m, 1H), 1.22 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 170.8 (C$_{quat}$), 170.7 (C$_{quat}$), 133.1 (C$_{quat}$), 122.2 (CH), 75.0 (CH), 61.6

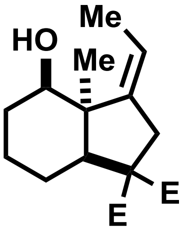
(CH_2), 61.5 (CH_2), 57.4 (C_{quat}), 42.9 (CH), 39.5 (CH), 30.5 (CH_2), 27.3 (CH_2), 23.8 (CH_2), 23.6 (CH_3), 23.0 (CH_2), 14.2 (CH_3), 14.1 (CH_3) ; **HRMS (EI)** m/z calcd for $C_{17}H_{26}O_5$ 310.1780, found 310.1762.



Bicyclo[3,4,0]alkenone (5.07b)

Bicyclo[3,4,0]alkenone (**5.07b**) was prepared according to the **general procedure G** Gold(I)-Catalyzed Carbocyclizationwith **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

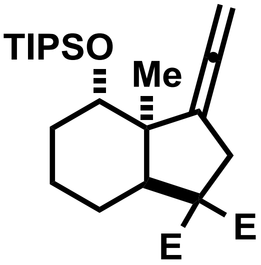
IR (neat, cm^{-1}) ν max 2981, 2939, 2867, 1733, 1707, 1447, 1256, 1051 ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.41 (qdd, J= 7.3 Hz, 2.0 Hz, 2.0 Hz, 1H), 4.25-4.08 (m, 4H), 3.40 (ddd, J = 17.7 Hz, 2.2 Hz, 2.2 Hz, 1H), 3.12 (dddd, J = 17.7 Hz, 1.8 Hz, 1.8 Hz, 1.0 Hz, 1H), 3.10-3.05 (m, 1H), 2.57-2.36 (m, 2H), 2.02-1.93 (m, 1H), 1.72-1.60 (m, 2H), 1.48 (ddd, J = 3.5 Hz, 1.8 Hz, 1.8 Hz, 1H), 1.45 (dt, J = 7.3 Hz, 2.1 Hz, 3H), 1.28 (dd, J= 7.1 Hz, 7.1 Hz, 3H), 1.28 (dd, J= 7.1 Hz, 7.1 Hz, 3H), 1.20 (s, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 213.1 (C_{quat}), 171.7 (C_{quat}), 169.7 (C_{quat}), 141.8 (C_{quat}), 119.5 (CH), 63.4 (C_{quat}), 61.9 (CH_2), 61.8 (CH_2), 59.2(C_{quat}), 56.4 (CH), 39.3 (CH_2), 39.0 (CH_2), 26.0 (CH_2), 24.8 (CH_2), 22.5 (CH_3), 14.1 (CH_3), 14.1 (CH_3), 13.3 (CH_3); **HRMS (EI)** m/z calcd for $C_{18}H_{26}O_5$ 322.1780, found 322.1767.



Bicyclo[3,4,0]alkenol (5.X6)

Bicyclo[3,4,0]alkenone **(5.X6)** l was prepared according to the general procedure for the reduction of ketone with NaBH$_4$ in MeOH/THF and isolated as a clear oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 5.56 (qdd, J= 7.3 Hz, 2.0 Hz, 2.0 Hz, 1H), 4.23-4.03 (m, 4H), 3.98 (t, J = 2.8 Hz, 1H), 3.04 (ddd, J = 15.7 Hz, 1.5 Hz, 1.5 Hz, 1H), 2.65 (t, J = 6.3 Hz, 1H), 2.56 (ddd, J = 15.7 Hz, 2.4 Hz, 2.4 Hz, 1H), 2.14 (br, 1H), 1.95-1.88 (m, 1H), 1.68 (ddd, J = 7.4 Hz, 2.3 Hz, 1.4 Hz, 3H), 1.75-1.66 (m, 1H), 1.64-1.51 (m, 3H), 1.24 (s, 3H), 1.20 (dd, J= 7.1 Hz, 7.1 Hz, 3H), 1.19 (dd, J= 7.1 Hz, 7.1 Hz, 3H), 1.24-1.19 (m, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 172.1 (C$_{quat}$), 171.4 (C$_{quat}$), 144.6 (C$_{quat}$), 119.1 (CH), 70.5 (CH), 61.4 (CH$_2$), 61.3 (CH$_2$), 61.3 (C$_{quat}$), 51.1 (CH), 48.1 (C$_{quat}$), 42.9 (CH$_2$), 25.6 (CH$_2$), 25.4 (CH$_3$), 21.5 (CH$_2$), 15.7 (CH$_2$), 14.1 (CH$_3$), 13.9 (CH$_3$) , 13.6 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{18}H_{28}O_5$ 324.1937, found 324.1927.

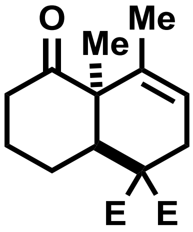


Bicyclo[3.4.0]alkenol (5.06b)

Bicyclo[3,4,0]alkenol (**5.06b**) was prepared according to the **general procedure N1** Siver(I)-Catalyzed Carbocyclization at 60°C with **tBuXPhos**AgNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2981, 2939, 2867, 1733, 1707, 1447, 1256, 1051 ; **^{1}H NMR (400MHz, CDCl$_3$)** δ = 4.76 (ddd, *J* = 3.2, 5.1, 9.4 Hz, 1 H), 4.68 (ddd, *J* = 3.4, 5.4, 9.2 Hz, 1 H), 4.29 - 4.04 (m, 4 H), 3.87 (dd, *J* = 3.4, 9.0 Hz, 1 H), 3.65 (td, *J* = 5.2, 17.2 Hz, 1 H), 2.90 - 2.85 (m, 1 H), 2.83 (td, *J* = 3.2, 17.2 Hz, 1 H), 1.65 - 1.43 (m, 5 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 1.14 - 0.98 (m, 25 H); **^{13}C NMR (75MHz, CDCl$_3$)** δ = 202.8 (C$_{quat}$), 172.6 (C$_{quat}$), 171.8 (C$_{quat}$), 107.4 (C$_{quat}$), 77.9 (CH$_2$), 71.2 (CH), 61.9

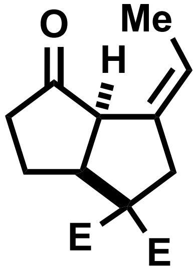
(CH$_2$), 61.7 (CH$_2$), 61.1 (C$_{quat}$), 50.9 (C$_{quat}$), 50.7 (CH), 36.2 (CH$_2$), 30.4 (CH$_2$), 22.7 (CH$_2$), 20.3 (CH$_2$), 18.4 (3xCH$_3$), 18.2 (3xCH$_3$), 17.8 (CH$_3$), 14.0 (CH$_3$), 14.0 (CH$_3$), 13.1 (3xCH); **HRMS (EI)** m/z calcd for $C_{24}H_{39}O_5Si$ [(M-iPr)$^+$] 435.2567, found 435.2563.



Bicyclo[4,4,0]alkenone (5.08b)

Bicyclo[4,4,0]alkenone (**5.08b**) was prepared according to the **general procedureN2** Silver(I)-Catalyzed Carbocyclization at 60°C with **JackiePhos**AgNCMeSbF$_6$ as catalyst and isolated as a clear oil.

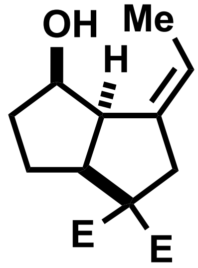
IR (neat, cm^{-1}) ν max 2981, 2940, 2867, 1735, 1722, 1447, 1233, 1095 ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.52 (ddq, J = 5.3 Hz, 2.6 Hz, 1.4 Hz, 1H), 4.25-4.01 (m, 4H), 2.84-2.80 (m, 1H), 2.53-2.37 (m, 2H), 2.32-2.26 (m, 2H), 2.02-1.94 (m, 2H), 1.68-1.59 (m, 2H), 1.46-1.43 (m, 3H), 1.26 (t, J = 7.2 Hz, 6H), 1.11 (s, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 212.8 (C$_{quat}$), 170.9 (C$_{quat}$), 170.5 (C$_{quat}$), 133.2 (CH), 120.9 (C$_{quat}$), 61.9 (CH$_2$), 61.9 (CH$_2$), 56.5 (C$_{quat}$), 55.0(C$_{quat}$), 47.4 (CH), 40.3 (CH$_2$), 26.9 (CH$_2$), 26.2 (CH$_2$), 25.2 (CH$_2$), 21.3 (CH$_3$), 19.3 (CH$_3$), 14.2/(CH$_3$), 14.1 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{18}H_{26}O_5$ 322.1780, found 322.1793



Bicyclo[3,3,0]alkenone (5.07c)

Bicyclo[3,3,0]alkenone (**5.07c**) was prepared according to the **general procedure G** Gold(I)-Catalyzed Carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

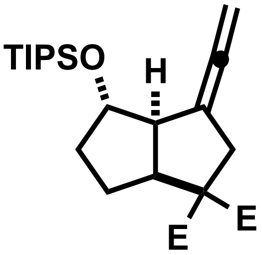
IR (neat, cm^{-1}) ν max 2980, 2937, 1734, 1464, 1256, 1191 ; **mp (°C)** 60.4-62.6 ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.58 (qdd, J= 7.0 Hz, 1.7 Hz, 1.7 Hz, 1H), 4.28-4.20 (m, 4H), 3.55-3.49 (m, 2H), 3.06 (ddd, J = 16.0 Hz, 2.7 Hz, 2.7 Hz, 1H), 2.66 (d, J = 16.0 Hz, 1H), 2.34-2.28 (m, 2H), 2.07-1.98 (m, 1H), 1.79 (dd, J = 6.4 Hz, 2.5 Hz, 3H), 1.52-1.45 (m, 1H), 1.27 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.23 (dd, J = 7.1 Hz, 7.1 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 216.1 (C$_{quat}$), 171.3 (C$_{quat}$), 169.5 (C$_{quat}$), 134.2 (C_{quat}), 123.1 (CH), 62.8 (C_{quat}), 61.7 (CH_2), 61.6 (CH_2), 53.6 (CH), 46.2 (CH), 39.4 (CH_2), 39.0 (CH_2), 23.0 (CH_2), 15.2 (CH_3), 14.3 (CH_3), 14.2 (CH_3),; **HRMS (EI)** m/z calcd for $C_{16}H_{22}O_5$ 294.1467 found 294.1452.



Bicyclo[3,3,0]alkenol (5.X7)

Bicyclo[3,3,0]alkenol **(5.X7)** was prepared according to a general procedure for the reduction of ketone with $NaBH_4$ in MeOH/THF and isolated as a clear oil.

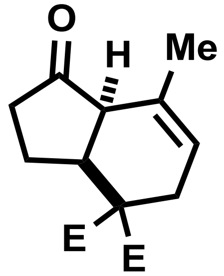
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (qdd, J= 6.7 Hz, 2.0 Hz, 2.0 Hz, 1H), 4.31 (dd, J = 5.9 Hz, 4.0 Hz, 1H), 4.22-4.05 (m, 4H), 3.33 (dd, J = 8.4 Hz, 8.4 Hz, 1H), 3.25-3.17 (m, 1H), 3.01 (ddd, J = 15.4 Hz, 2.6 Hz, 2.6 Hz, 1H), 2.57 (d, J = 15.4, 1H), 1.88-1.83 (m, 2H), 1.69-1.42 (m, 3H), 1.59 (dd, J = 6.7 Hz, 3.0 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 172.0 (C_{quat}), 170.0 (C_{quat}), 138.4 (C_{quat}), 120.4 (CH), 72.7 (CH), 61.4 (C_{quat}), 61.4 (CH_2), 61.2 (CH_2), 51.1 (CH), 49.2 (CH), 41.5 (CH_2), 36.0 (CH_2), 26.3 (CH_2), 14.5 (CH_3), 14.2 (CH_3), 14.1 (CH_3),; **HRMS (EI)** m/z calcd for $C_{16}H_{24}O_5$ 296.1624 found 296.1636.



Bicyclo[3.3.0]alkenol (5.06c)

Bicyclo[3,3,0]alkenone (**5.06c**) was prepared according to the **general procedure N1** Silver(I)-Catalyzed Carbocyclization at 60°C with **tBuXPhos**AgNCMeSbF$_6$ as catalyst and isolated as a clear oil.

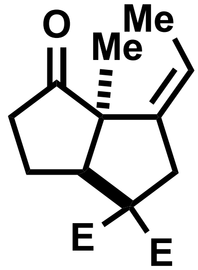
IR (neat, cm^{-1}) ν max 2984, 2938, 2888, 1742, 1456, 1222 ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 4.76-4.67 (m, 2H), 4.26-4.14 (m, 4H), 3.37-3.31 (m, 1H), 3.29-3.24 (m, 1H), 3.10 (dddd, J = 16.5 Hz, 6.1 Hz, 6.1 Hz, 2.1 Hz, 1H), 2.74 (ddd, J = 16.5 Hz, 2.5 Hz, 2.5 Hz, 1H), 2.00 (dq, 13.3 Hz, 8,9 Hz, 1H), 1.81-1.72 (m, 1H), 1.66-1.59 (m, 1H), 1.27-1.17 (m, 2H), 1.24 (q, J = 7.2 Hz, 6H), 1.04 (s, 21H)). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 203.0 (C$_{quat}$), 171.8 (C$_{quat}$), 170.4 (C$_{quat}$), 101.4 (C$_{quat}$), 80.4 (CH), 77.3 (CH$_2$), 64.2 (C$_{quat}$), 61.6 (CH$_2$), 61.4 (CH$_2$), 56.9 (CH), 47.2 (CH), 36.8 (CH$_2$), 35.3 (CH$_2$), 26.1 (CH$_2$), 18.2 (CH$_3$*6), 14.3 (CH$_3$), 14.1 (CH$_3$), 12.3 (CH*3) **; HRMS (EI)** m/z calcd for $C_{25}H_{42}O_5Si$ $[(M-C_3H_7)^+]$ 405.2254 found 407.2265



Bicyclo[4,3,0]alkenone (5.08c)

Bicyclo[4,3,0]alkenone (**5.08c**) was prepared according to the **general procedure N2** Silver(I)-Catalyzed Carbocyclization at 60°C with **JackiePhos**AgNCMeSbF$_6$ as catalyst and isolated as a clear oil.

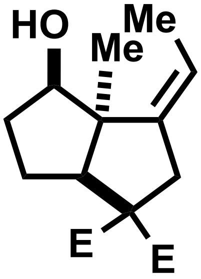
IR (neat, cm^{-1}) ν max 2982, 2940, 2867, 1746, 1733, 1464, 1256 ; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.40 (ddt, J = 3.6 Hz, 2.3 Hz, 1.4 Hz, 1H), 4.25-.4.05 (m, 4H), 3.15 (dt, J = 12.1 Hz, 7.3 Hz, 1H), 3.07-2.99 (m, 1H), 2.67-2.58 (m, 2H), 2.22-2.11 (m, 2H), 1.85-1.78 (m, 1H), 1.74 (dd, J = 7.0 Hz, 2.8 Hz, 3H), 1.50-1.41 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 215.8 (C$_{quat}$), 170.8 (C$_{quat}$), 170.4 (C$_{quat}$), 128.8 (C$_{quat}$), 120.0 (CH), 61.5 (CH$_2$), 61.5 (CH$_2$), 54.9 (C$_{quat}$), 52.8 (CH), 39.9 (CH), 36.9 (CH$_2$), 26.1 (CH$_2$), 22.9 (CH$_2$), 21.0 (CH$_3$), 14.1 (CH$_3$), 14.0 (CH$_3$)**; HRMS (EI)** m/z calcd for $C_{16}H_{22}O_5$ 294.1467 found 294.1463.



Bicyclo[3.3.0]alkenone (5.07d)

Bicyclo[3,3,0]alkenone (**5.07d**) was prepared according to the **general procedure G** Gold(I)-Catalyzed Carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm^{-1}) ν max 2980, 2937, 2890, 1734, 1464, 1256, 1097; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.48 (qdd, J= 7.4 Hz, 1.8 Hz, 1.8 Hz, 1H), 4.23-4.22 (m, 4H), 3.19-3.16 (m, 1H), 3.14-3.11 (m, 1H), 2.97 (dq, J = 17.1 Hz, 1.3 Hz, 1H), 2.36 (dd, J = 9.3 Hz, 3.7 Hz, 1H), 2.34 (dd, J = 9.3 Hz, 3.7 Hz, 0.5H), 2.26-2.12 (m, 1H), 1.99 (ddddd, J = 13.3 Hz, 9.4 Hz, 3.7 Hz,0.9 Hz, 1H), 1.68 (ddd, J = 7.4 Hz, 2.7 Hz, 1.3 Hz, 3H), 1.55-1.44 (m, 1H), 1.29 (s, 3H), 1.22 (t, J = 7.1 Hz, 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 7.1 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 217.6 (C$_{quat}$), 171.0 (C$_{quat}$), 169.6 (C$_{quat}$), 138.6 (C$_{quat}$), 123.0 (CH), 62.1 (C$_{quat}$), 61.8 (CH$_2$), 61.6 (CH$_2$), 59.1 (C$_{quat}$), 55.6 (CH), 39.9 (CH$_2$), 37.0 (CH$_2$), 22.1(CH$_3$), 22.0 (CH$_2$), 14.2 (CH$_3$), 14.0 (CH$_3$), 13.7 (CH$_3$); **HRMS (EI)** m/z calcd for [M$^+$] C$_{17}$H$_{24}$O$_5$ 308.1624 found 308.16345.

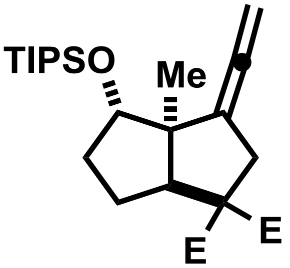


Bicyclo[3,3,0]alkenol (5.X8)

Bicyclo[3,4,0]alkenol **(5.X8)** was prepared according to the general procedure for the reduction of ketone with NaBH$_4$ in MeOH/THF and isolated as a clear oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ 5.33 (qdd, J= 7.3 Hz, 2.7 Hz, 0.9 Hz, 1H), 4.26-4.12 (m, 4H), 4.11-4.07 (m, 1H), 3.11 (ddd, J =16.5 Hz, 2.8 Hz, 2.8 Hz, 1H), 3.03 (td, J = 7.7 Hz, 1.2 Hz, 1H), 2.82 (d, J = 16.5 Hz, 1H), 1.96-1.84 (m, 2H), 1.69 (ddd, J = 7.7 Hz, 2.8 Hz, 1.0 Hz, 3H), 1.62-1.52 (m, 3H), 1.33

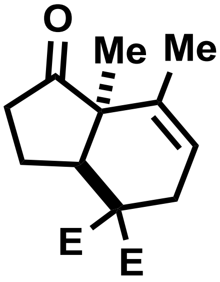
(s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 171.7 (C$_{quat}$), 170.4 (C$_{quat}$), 145.8 (C$_{quat}$), 118.1 (CH), 81.2 (CH), 62.2 (C$_{quat}$), 61.6 (CH$_2$), 61.4 (CH$_2$), 56.9 (CH), 55.6 (C$_{quat}$), 41.6 (CH$_2$), 34.9 (CH$_2$), 25.2 (CH$_2$), 20.1 (CH$_3$), 14.5 (CH$_3$), 14.3 (CH$_3$), 14.2 (CH$_3$),**;** **HRMS (EI)** m/z calcd for $C_{17}H_{26}O_5$ 310.1780 found 310. 1780



Bicyclo[3.3.0]alkenol (5.06d)

Bicyclo[3,3,0]alkenol (**5.06d**) was prepared according to the **general procedure N1** Silver(I)-Catalyzed Carbocyclization at 60°C with **tBuXPhos**AgNCMeSbF$_6$ as catalyst and isolated as a clear oil.

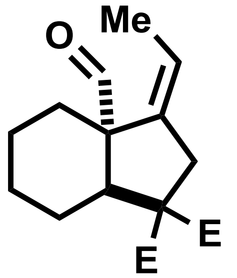
IR (neat, cm^{-1}) ν max 2980, 2937, 2890, 1745, 1464, 1256, 1097; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 4.79 (ddd, J = 9.7 Hz, 5.6 Hz, 1.4 Hz, 1H), 4.60 (ddd, J = 9.7 Hz, 6.0 Hz, 1.6 Hz, 1H), 4.24-4.12 (m, 4H), 3.88 (dd, J = 8.2 Hz, 4.6 Hz, 1H), 3.13 (dt, J = 15.5 Hz, 5.8 Hz, 1H), 3.01 (t, J = 8.7 Hz, 1H), 2.84 (dd, J = 15.4 Hz, 1.4 Hz, 1H), 1.88-1.77 (m, 2H), 1.66-1.56 (m, 2H), 1.23 (t, J = 7.4 Hz, 6H), 1.17 (s, 3H), 1.07-1.04 (m, 2H) **^{13}C NMR (100 MHz, CDCl$_3$)** δ 202.51 (C$_{quat}$), 171.4 (C$_{quat}$), 170.1 (C$_{quat}$), 107.9 81.4 (CH), 78.1 (CH$_2$), 63.2 (C$_{quat}$), 61.7 (CH$_2$), 61.5 (CH$_2$), 55.7 (C$_{quat}$), 53.1 (CH), 37.5 (CH$_2$), 34.6 (CH$_2$), 24.8 (CH$_2$), 20.4 (CH$_3$), 18.3 (CH$_3$), 14.3 (CH$_3$), 14.2 (CH$_3$), 12.6 (CH) **; HRMS (EI)** m/z calcd for [M$^+$] $C_{27}H_{46}O_4Si$ [(M-iPr)$^+$] =419.2618 found 419.2637.



Bicyclo[4.3.0]alkenone (5.08d)

Bicyclo[4,3,0]alkenone (**5.08d**) was prepared according to the **general procedure N2** Silver(I)-Catalyzed Carbocyclization at 60°C with **JackiePhos**AgNCMeSbF$_6$ as catalyst and isolated as a clear oil.

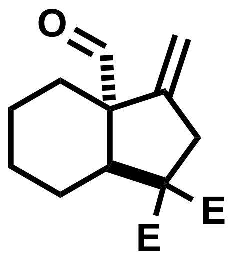
IR (neat, cm^{-1}) ν max 2984, 2941, 2866, 1743, 1733, 1464 1256; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.51 (ddd, J = 5.4 Hz, 1.9 Hz, 1.9 Hz, 1H), 4.26-4.06 (m, 4H), 2.97 (dd, J = 11.5 Hz, 6.7 Hz, 1H), 2.91 (dddd, J = 18.4 Hz, 5.8 Hz, 1.1 Hz, 1.1 Hz, 1H), 2.45-2.21 (m, 4H), 1.68-1.59 (m, 1H), 1.58 (ddd, J = 2.6 Hz, 1.4 Hz, 1.4 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.13 (s, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 217.5 (C$_{quat}$), 170.3 (C$_{quat}$), 170.1 (C$_{quat}$), 131.2 (C$_{quat}$), 121.9 (CH), 61.5 (CH$_2$x2), 54.4 (C$_{quat}$), 53.5 (C$_{quat}$), 46.8 (CH), 35.2 (CH$_2$), 26.8 (CH$_2$), 21.9 (CH$_2$), 21.6 (CH$_3$), 18.3 (CH$_3$), 14.0 (CH$_3$), 13.8 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{17}H_{24}O_5$ [M$^+$] 308.1624 found 308.1633.



Bicyclo[3,4,0]alkenone (5.X9)

Bicyclo[3,4,0]alkenone **(5.X9)** was prepared according to the **general procedure G** Gold(I)-Catalyzed Carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

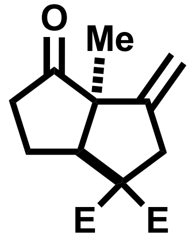
^{1}H NMR (400 MHz, CDCl$_3$) δ 9.38 (d, J = 1.3 Hz, 1H), 5.59 (ddq, J = 7.3 Hz, 2.1 Hz, 2.1 Hz, 1H), 4.32-4.06 (m, 4H), 3.23 (ddd, J = 16.8 Hz, 1.8 Hz, 1.8 Hz, 1H), 2.63 (ddd, J = 16.8 Hz, 2.4 Hz, 2.4 Hz, 1H), 3.14, 2.25, 1.93-1.86 (m,1H), 1.55 (dd, J =7.3 Hz, 2.0 Hz, 2.0 Hz, 3H), 1.34-1.51 (m, 3H), 1.28 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.26 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.04 (s, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 200.5 (CH), 171.8 (C$_{quat}$), 171.4 (C$_{quat}$), 139.1 (C$_{quat}$), 122.0 (CH), 61.8 (CH$_2$), 61.7 (CH$_2$), 60.8 (C$_{quat}$), 59.2 (C$_{quat}$), 45.1 (CH), 42.1 (CH$_2$), 26.2 (CH$_2$), 23.5 (CH$_2$), 21.1 (CH$_2$), 21.0 (CH$_2$), 17.8 (CH), 14.1 (CH$_3$), 14.1 (CH$_3$), 13.9 (CH$_3$), **: HRMS (EI) m**/z calcd for $C_{18}H_{26}O_5$ [(M-CO)] 293.1753, found 322.1727.



Bicyclo[3.4.0]alkenone (5.X10)

Bicyclo[3,4,0]alkenone **(5.X10)** was prepared according to the **general procedure G** Gold(I)-Catalyzed Carbocyclization with **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

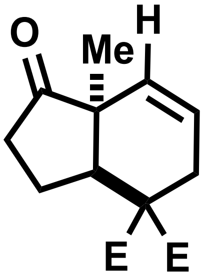
^{1}H NMR (400 MHz, CDCl$_3$) δ 9.33 (s, 1H), 5.25 (dd, J = 2.1 Hz, 2.1 Hz, 1H), 4.89 (dd, J = 2.5 Hz, 2.5 Hz, 1H), 4.28-4.18 (m, 2H), 4.18-4.06 (m, 2H), 3.35 (ddd, J = 18.0 Hz, 2.1 Hz, 2.1 Hz, 1H), 3.16-3.13 (m, 1H), 2.82 (ddd, J = 18.0 Hz, 2.4 Hz, 2.4 Hz, 1H), 1.78 (ddd, J = 9.3 Hz, 4.5 Hz, 4.5 Hz, 1H), 1.63-1.27 (m, 7H), 1.24 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.21 (dd, J = 7.1 Hz, 7.1 Hz,, 3H) ; **^{13}C NMR (100 MHz, CDCl$_3$)** δ 200.7 (CH), 171.7 (C$_{quat}$), 170.2 (C$_{quat}$), 146.4 (C$_{quat}$), 110.5 (CH$_2$), 61.9 (CH$_2$), 61.8 (CH$_2$), 61.7 (C$_{quat}$), 61.4 (C$_{quat}$), 44.0 (CH), 38.5 (CH$_2$), 27.2 (CH$_2$), 24.0 (CH$_2$), 23.0 (CH$_2$), 20.6 (CH$_2$), 14.1 (CH$_3$), 14.0 (CH$_3$), ; **HRMS (EI)** m/z calcd for $C_{17}H_{24}O_5$ [(M-$C_{16}H_{23}O_4$)$^+$] 279.1596, found 279.1578.



Bicyclo[3.3.0]alkenone (5.X11)

Bicyclo[3,3,0]alkenone **(5.X11)** was prepared according to the **general procedure G** Gold(I)-Catalyzed Carbocyclizationwith **IPr**AuNCMeSbF$_6$ as catalyst and isolated as a clear oil.

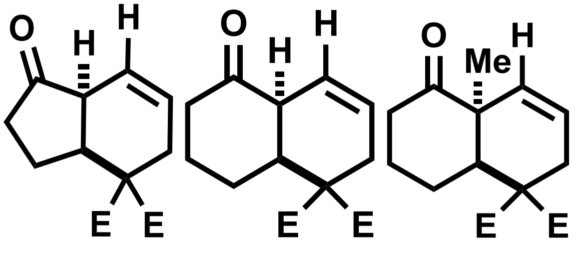
IR (neat, cm-1) ν max 1742, 1730; **^{1}H NMR (400MHz, CDCl$_3$)** δ = 5.05 - 5.00 (m, 2 H), 4.26 - 4.12 (m, 4 H), 3.30 - 3.18 (m, 2 H), 3.05 - 2.98 (m, 1 H), 2.40 - 2.23 (m, 2 H), 2.09 - 2.00 (m, 1 H), 1.55 - 1.42 (m, 1 H), 1.23 (s, 3 H), 1.25 (dt, *J* = 4.0, 7.1 Hz, 6 H); **^{13}C NMR (101MHz, CDCl$_3$)** δ = 217.8 (C$_{quat}$), 171.1 (C$_{quat}$), 169.6 (C$_{quat}$), 149.3 (C$_{quat}$), 110.2 (CH$_2$), 62.3 (C$_{quat}$), 61.9 (CH$_2$), 61.8 (CH$_2$), 59.7 (C$_{quat}$), 53.3 (CH), 38.8 (CH$_2$), 37.3 (CH$_2$), 24.0 (CH$_3$), 22.4 (CH$_2$), 14.2 (CH$_3$), 14.1 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{16}H_{22}O_5$ [(M)$^+$] 294.1467, found 294.1467.



Bicyclo[4.3.0]alkenone (5.10b) (Patrick Leveque master work)

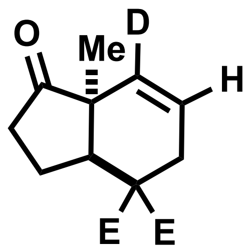
Bicyclo[4,3,0]alkenone (**5.10b**) was prepared according to the **general procedure O** Copper(I)-Catalyzed Carbocyclization at 60°C with **Me_4tBuXPhos**CuNCMeSbF_6 as catalyst and isolated as a clear oil. Characterized as an inseparable mixture of the 6-endo-dig product bicyclo[4,3,0]alkenone (**5.10b**) and the 5-exo dig product bicyclo[3,3,0]alkenone.

IR (neat, cm^{-1}) ν max 2973, 2941, 2856, 1741, 1732, 1468 1256; **^{1}H NMR (400MHz, $CDCl_3$)** δ = 5.74 (ddd, *J* = 2.2, 5.7, 10.0 Hz, 1 H), 5.26 (td, *J* = 1.4, 10.0 Hz, 1 H), 4.27 - 4.07 (m, 4 H), 3.05 - 2.98 (m, 2 H), 2.43 - 2.16 (m, 4 H), 1.61 - 1.40 (m, 1 H), 1.25 (dt, *J* = 4.0, 7.0 Hz, 6 H), 1.11 (s, 3 H); **^{13}C NMR (101MHz, $CDCl_3$)** δ = 218.8 (C_{quat}), 170.3 (C_{quat}), 170.2 (C_{quat}), 127.3 (CH), 125.1 (CH), 61.8 (2xCH_2), 54.7 (C_{quat}), 51.3 (C_{quat}), 45.5 (CH), 35.8 (CH_2), 26.2 (CH_2), 23.3 (CH_3), 22.4 (CH_2), 14.2 (CH_3), 14.1 (CH_3); **HRMS (EI)** m/z calcd for $C_{16}H_{22}O_5$ [$(M)^+$] 294.1467, found 294.1471



Bicycloalkenones (5.10a, c,d) [1]

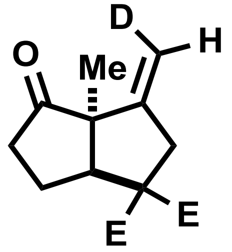
Bicycloalkenones was prepared according to **general procedure G or O** Gold(I) or Copper(I)-Catalyzed Carbocyclization and isolated as a colorless oil. Exhibited spectral data are in accordance with previous reported.



Bicyclo[4.3.0]alkenone (5.10h)

Bicyclo[4,3,0]alkenone (**5.23**) was prepared according to the **general procedure O** at rt with **Me$_4$tBuXPhos**CuNCMeSbF$_6$ as catalyst and D_2O instead of H_2O and isolated as a clear oil. Bicycloalkenones (**5.22)** and **(5.23)** was isolated as a clear oil and characterized as an inseparable mixture.

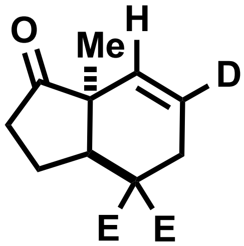
IR (neat, cm-^{1}) ν max 2985, 2938, 2877, 1746, 1733, 1464, 1256; **^{1}H NMR (400MHz, CDCl$_3$)** δ 5.76-5.71 (m, 2H), 4.27 - 4.07 (m, 4 H), 3.05 - 2.98 (m, 1 H), 2.88 (d, J = 18.4 Hz, 1H), 2.43 - 2.16 (m, 4 H), 1.61 - 1.40 (m, 1 H), 1.25 (dt, *J* = 4.0, 7.0 Hz, 6 H), 1.11 (s, 3 H); **^{13}C NMR (101MHz, CDCl$_3$)** δ 218.8 (C_{quat}), 170.3 (C_{quat}), 170.2 (C_{quat}), 127.3 (CH), 124.8 (t, J = 24.6 Hz, CD), 61.8 (2xCH_2), 54.7 (C_{quat}), 51.3 (C_{quat}), 45.5 (CH), 35.8 (CH_2), 26.2 (CH_2), 23.3 (CH_3), 22.4 (CH_2), 14.2 (CH_3), 14.1 (CH_3); **HRMS (EI)** m/z calcd for $C_{16}H_{21}DO_5$ [$(M)^+$] 295.1530, found 295.1523



Bicyclo[3.3.0]alkenone (5.11h)

Bicyclo[3,3,0]alkenone (**5.11i**) was prepared according to the **general procedure O** at rt with **Me$_4$tBuXPhos**CuNCMeSbF$_6$ as catalyst and isolated as a clear oil. Bicycloalkenones (**5.21)** and **(5.24)** was isolated as a clear oil and characterized as an inseparable mixture.

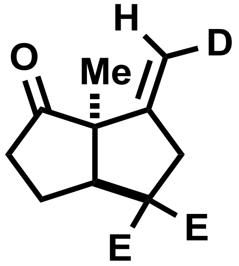
.IR (neat, cm^{-1}) ν max 2980, 2937, 1734, 1464, 1256, 1191; **^{1}H NMR (400MHz, CDCl$_3$)** δ = 5.02 (d, J = 7.1 Hz, 1H), 4.26 - 4.07 (m, 4 H), 3.27 (t, J = 8.8 Hz, 1H), 3.19 (d, 2.8 Hz, 1H), 3.05 - 2.98 (m, 1 H), 2.40 - 2.23 (m, 2 H), 2.09 - 2.00 (m, 1 H), 1.55 - 1.42 (m, 1 H), 1.23 (s, 3 H), 1.25 (dt, *J* = 4.0, 7.1 Hz, 6 H); **^{13}C NMR (101MHz, CDCl$_3$)** δ = 217.8 (C_{quat}), 171.1 (C_{quat}), 169.6 (C_{quat}), 149.2 (C_{quat}), 109.9 (t, J = 23.1 Hz, CHD), 62.3 (C_{quat}), 61.9 (CH_2), 61.8 (CH_2), 59.7 (C_{quat}), 53.3 (CH), 38.8 (CH_2), 37.3 (CH_2), 24.0 (CH_3), 22.4 (CH_2), 14.2 (CH_3), 14.1 (CH_3); **HRMS (EI)** m/z calcd for $C_{16}H_{21}DO_5$ $[(M)^+]$ 295.1530, found 295.1523



Bicyclo[4.3.0]alkenone (5.10i)

Bicyclo[4,3,0]alkenone (**5.10j**) was prepared according to the **general procedure O** at rt with **Me$_4$tBuXPhos**CuNCMeSbF$_6$ as catalyst and D_2O instead of H_2O and isolated as a clear oil. Bicycloalkenones (**5.22)** and **(5.23)** was isolated as a clear oil and characterized as an inseparable mixture.

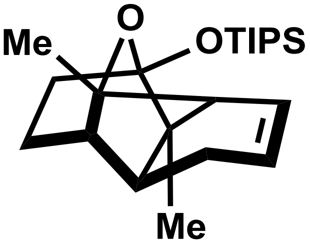
IR (neat, cm-^{1}) ν max 2983, 2931, 2862, 1743, 1733, 1464 1256; **^{1}H NMR (400MHz, CDCl$_3$)** δ 5.25 (br, 1 H), 4.27 - 4.07 (m, 4 H), 3.05 - 2.98 (m, 1 H), 2.88 (d, J = 18.4 Hz, 1H), 2.43 - 2.16 (m, 4 H), 1.61 - 1.40 (m, 1 H), 1.25 (dt, *J* = 4.0, 7.0 Hz, 6 H), 1.11 (s, 3 H); **^{13}C NMR (101MHz, CDCl$_3$)** δ 218.8 (C_{quat}), 170.3 (C_{quat}), 170.2 (C_{quat}), 127.3 (CH), 124.8 (t, J = 24.6 Hz, CD), 61.8 (2xCH_2), 54.7 (C_{quat}), 51.3 (C_{quat}), 45.5 (CH), 35.8 (CH_2), 26.2 (CH_2), 23.3 (CH_3), 22.4 (CH_2), 14.2 (CH_3), 14.1 (CH_3); **HRMS (EI)** m/z calcd for $C_{16}H_{21}DO_5$ $[(M)^+]$ 295.1530, found 295.1518



Bicyclo[3.3.0]alkenone (5.11i)

Bicyclo[3,3,0]alkenone (**5.11j**) was prepared according to the **general procedure O** at rt with **Me$_4$tBuXPhos**CuNCMeSbF$_6$ as catalyst and isolated as a clear oil. Bicycloalkenones (**5.22)** and **(5.23)** was isolated as a clear oil and characterized as an inseparable mixture.

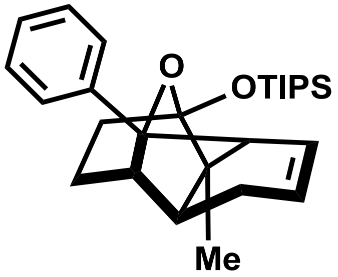
.IR (neat, cm^{-1}) ν max 2982, 2927, 2893, 1734, 1464, 1266, 1097; **^{1}H NMR (400MHz, CDCl$_3$)** δ = 5.00 (dd, J =2.8 Hz, 1.8 Hz, 1H), 4.26 - 4.07 (m, 4 H), 3.27 (t, J = 8.8 Hz, 1H), 3.20 (dd, J = 17.3 Hz, 2.8 Hz, 1H), 3.05 - 2.98 (m, 1 H), 2.40 - 2.23 (m, 2 H), 2.09 - 2.00 (m, 1 H), 1.55 - 1.42 (m, 1 H), 1.23 (s, 3 H), 1.25 (dt, *J* = 4.0, 7.1 Hz, 6 H); **^{13}C NMR (101MHz, CDCl$_3$)** δ = 217.8 (C$_{quat}$), 171.1 (C$_{quat}$), 169.6 (C$_{quat}$), 149.3 (C$_{quat}$), 109.9 (t, J = 23.1 Hz, CHD), 62.3 (C$_{quat}$), 61.9 (CH$_2$), 61.8 (CH$_2$), 59.7 (C$_{quat}$), 53.3 (CH), 38.8 (CH$_2$), 37.3 (CH$_2$), 24.0 (CH$_3$), 22.4 (CH$_2$), 14.2 (CH$_3$), 14.1 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{16}H_{21}DO_5$ [(M)$^+$] 295.1530, found 295.1518



Polycyclicalkene (5.12e)

Polycyclicalkene **(5.12e)** was prepared according to the **general procedure N1 or O** Siver(I) or Copper(I)-Catalyzed Carbocyclization at 60°C with **tBuXPhos**AgNCMeSbF$_6$ or **tBuXPhos**CuNCMeSbF as catalyst and isolated as a clear oil.

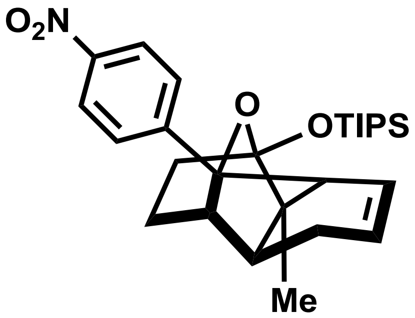
IR (neat, cm-^{1}) ν max 2945, 2866, 1460, 1379, 1242, 1049; **^{1}H NMR (400MHz, CDCl$_3$)** δ 5.65-5.55 (m, 2H), 2.32 (ddd, J = 18.7 Hz, 3.8 Hz, 2.1 Hz, 2.1 Hz, 1H), 1,99 (dd, J = 6.5 Hz, 1.3 Hz, 1H), 1.91-1.84 (m, 2H), 1.67-1.64 (m, 2H), 1.62-1.55 (m, 1H), 1.46-1.43 (m, 2H), 1.20 (s, 3H), 1.11-1.05 (m, 21H), 1.01 (s, 3H) ; **^{13}C NMR (101MHz, CDCl$_3$)** δ 125.6 (CH), 125.5 (CH), 104.6 (C$_{quat}$), 93.3 (C$_{quat}$), 53.1 (C$_{quat}$), 52.4 (CH), 46.7 (CH), 43.3 (CH), 30.7 (CH$_2$), 29.9 (CH$_2$), 23.0 (CH$_2$), 18.4 (CH$_3$*6), 16.6 (CH$_3$), 13.4 (CH*3), 11.0 (CH$_3$); **HRMS (EI)** m/z calcd for $C_{22}H_{38}O_2Si$ [(M)$^+$] 362.2641, found 362.2659



Polycyclicalkene (5.12f)

Polycyclicalkene **(5.12f)** was prepared according to the **general procedure N1** Siver(I)-Catalyzed Carbocyclization at 60°C with **tBuXPhos**AgNCMeSbF$_6$ as catalyst and isolated as a clear oil.

IR (neat, cm-^{1}) ν max 2975, 2862, 1461, 1242, 1195; **^{1}H NMR (400MHz, CDCl$_3$)** 7.52–7.48 (μ, 2H), 7.30-7.20 (m, 3H), 5.69 (dddd, J = 9.5 Hz, 3.7 Hz, 2.7 Hz, 0.8 Hz, 1H), 5.55 (tdd, J = 9.3 Hz, 7.1 Hz, 2.0 Hz, 1H), 2.43 (dddd, J = 18.9 Hz, 9.6 Hz, 2.4 Hz, 2.4 Hz, 1H), 2.29 (dd, J = 6.9 Hz, 1.7 Hz, 1H), 2.09 (dddd, J = 18.9 Hz, 3.9 Hz, 1.9 Hz, 19 Hz, 1H), 2.05-1.98 (m, 2H), 1.83-1.77 (m, 2H), 1.62-1.54 (m, 1H), 1.51-1.42 (m, 1H), 1.24-1.14 (m, 3H). 1.12-1.07 (m, 21H) **^{13}C NMR (101MHz, CDCl$_3$)** δ 140.0 (C$_{quat}$), 127.9 (C$_{quat}$), 127.0 (CH*2), 125. 9 (CH), 125.8 (CH), 125.7 (CH*2), 104.4 (C$_{quat}$), 95.7 (C$_{quat}$), 54.7 (C$_{quat}$), 54.4 (CH), 49.2 (CH), 43.3 (CH), 31.0 (CH$_2$), 30.2 (CH$_2$), 223.0 (CH$_2$), 18.3 (CH$_3$*6), 13.2 (CH$_3$), 10.7 (CH*3) ; **HRMS (EI)** m/z calcd for $C_{27}H_{40}O_2Si$ [(M)$^+$] 424.2798, found 424.2764



Polycyclicalkene (5.12f)

Polycyclicalkene **(5.12eg** was prepared according to the **general procedure N1** Siver(I)-Catalyzed Carbocyclization at 60°C with **tBuXPhos**AgNCMeSbF$_6$ as catalyst and isolated as a clear oil. The intermediate was purified by flash chromatography with neutralized silica (Et$_3$N).

IR (neat, cm-^{1}) ν max 2977, 2873, 1465, 1242, 1192, 888; **^{1}H NMR (400MHz, CDCl$_3$)** δ 8.16 (dt, J = 8.9 Hz, 2.4 Hz, 2H), 7.67 (dt, 8.9 Hz. 2.4 Hz, 2H), 5.74 (dt, J = 9.8 Hz, 2.9 Hz, 1H), 5.54 (tdd, J = 19.1

Hz, 4.5 Hz, 2.3 Hz, 1H), 2.49 (dtd, J = 19.1 Hz, 4.5 Hz, 2.3 Hz, 1H), 2.32 (dd, J = 6.9 Hz, 1.8 Hz, 1H), 2.15 (dtd, J = 19.1 Hz, 3.9 Hz, 2.0 Hz, 1H), 2.05-1.98 (m, 2H), 1.89-1.81 (m, 2H), 1.57-1.51 (m, 3H), 1.22-1.16 (m, 2H), 1.15-1.11 (m, 21H) **^{13}C NMR (101MHz, $CDCl_3$)** δ 147.6 (C_{quat}), 147.1 (C_{quat}), 126.9 (CH*2), 126. 4 (CH), 125.1 (CH*2), 123.2 (CH), 104.8 (C_{quat}), 95.2 (C_{quat}), 55.3 (C_{quat}), 54.8 (CH), 49.8 (CH), 43.0 (CH), 31.0 (CH_2), 30.1 (CH_2), 23.0 (CH_2), 18.3 (CH_3*6), 13.2 (CH_3), 10.9 (CH*3) ; **HRMS (EI)** m/z calcd for $C_{27}H_{39}O_4NSi$ [$(M - C_3H_7)^+$] 426.2698, found 426.2036

References

(1) Kusama, H.; Yamabe, H.; Iwasawa, N. *Org. Lett.* **2002**, 4, 2569

Glossary of abbreviations

%VBur percent buried volume
Au gold
Ac acetate
Ag silver
AIBN 2,2’-azobis(2-methylpropionitrile)
BArF tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAP 2,2’-bis(diphenylphosphanyl)-1,1’-binaphthalene
Binol 1,1'-bi-2-naphthol
Bn benzyl
Bu butyl
Bu_3SnH tributyl tin(IV) hydride
Bz benzoyl
CAN ammonium cerium nitrate
CoA coenzyme-A
$Co_2(CO)_6$
Chiral PTC chiral phase-transfert catalyst
CSA 10-camphorsulfonic acid
Cu copper
D.-A. Diels-Alder
dba trans,trans-dibenzylideneacetone
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE dichloroethane
DCM dichloromethane
DIBAL-H diisobutylaluminum hydride
Dig diagonal
DMAP 4-dimethylaminopyridine
DMAPP dimethylallyl diphosphate
DMDO dimethyldioxirane
DMP Dess-Martin periodinane
DMS dimethyl sulfide
DMSO dimethyl sulfoxide
dppf 1,1’-bis(diphenylphosphanyl)ferrocene
Et ethyl
Et_2AlCl diethylaluminium(III) chloride
eV electron-volt
HCl hydrochloric acid
HFIP 1,1,1,3,3,3-hexafluoro-2-propanol
Hg mercury
HIV *Human immunodeficiency virus*
HMPA hexamethylphosphoramide
KHMDS potassium hexamethyldisilazide
IC50 concentration of inhibitor required for 50% inhibition of target

IPr 1,3-bis(2,6-diisopropylphenyl)imidazolium
LBA lewis acid assisted Bronsted acid
LC50 (Lethal Concentration 50) is the concentration of a chemical which kills
LDA lithium diisopropylamide
LiHMDS lithium hexamethyldisilazide
LiTMP lithium tetramethylpiperidide
LM+ [LMNCMe]SbF_6 (M = Au, Ag, Cu)
m-CPBA meta-chloroperoxybenzoic acid
Me methyl
MeI methyl iodide
MPAP monocyclic polyprenylated acylphloroglucinols
MOM methoxymethyl
Ms methanesulfonyl
OsO_4 osmium tetraoxide
NaHMDS sodium hexamethyldisilazide
NBS N-bromosuccinimide
NHC N-heterocyclic carbine
NIS N-iodosuccinimide
NMO 4-methylmorpholine-N-oxide
NMR nuclear magnetic resonance
o-DCB 1,2-dichlorobenzene
OsO_4 osmium tetroxyde
$Pb(OAc)_4$ lead(IV) acetate
PCC pyridinium chlorochromate
PDC pyridinium dichromate
Ph phenyl
Ph. D. philosophy doctorate
PPAP polycyclic polyprenylated acylphloroglucinol
PPh_3 triphenylphosphine
PhO)$_3$P triphenylphosphite
Pr propyl
Pt platine
RCM ring closing metathesis
SOMO single occupied molecular orbital
$SnCl_4$ tin(IV) tetrachloride
p-TsOH para-toluenesulfonic acid
TBAB tetra-n-butylammonium bromide
TBAF tetra-n-butylammonium fluoride
TBDPS tert-butyldiphenylsilyl
TBHP tert-butyl hydroperoxide
TBS tert-butyldimethylsilyl
TEMPO 2,2,6,6-tetramethylpiperidine 1-oxide
TIPS tri-isopropylsilyl
Tf trifluoromethanesulfonyl
TFA trifluoroacetic acid
TFAA trifluoroacetic anhydride

THF tetrahydrofuran
TIPS triisopropylsilyl
TMEDA tetramethylethylenediamine
TMS trimethylsilyl
TS transition state

Electronic Supporting Information

1. Proton and Carbon spectra of all new compounds

2 X-ray data

3. Electronic Thesis