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REVIEW

Strategic innovation in the total synthesis of complex natural products using gold catalysis

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Covering: XXXX to YYYY / up to YYYY / up to the end of YYYY

Novel organic reactions drive the advance of chemical synthesis in the same way that enabling technologies drive new scientific discoveries. One area of organic methodology that has undergone significant growth during the last decade is that of homogeneous gold-catalyzed transformations. This trend has been further enhanced by the employment of gold catalysis on a routine basis to accomplish the total synthesis of natural products. In particular, the superior π acidity of the cationic gold complex for the activation of alkynes and allenes towards nucleophilic addition has significantly enriched the toolkit of transformations available to the total synthesis community, and inspired a new era of creativity in terms of the strategic disconnection of target compounds during their retrosynthetic analysis. Instead of simply supplementing the many existing reviews of gold catalysis, this review has been organized from the perspective of synthetic target families, with particular emphasis on the use of gold-catalyzed transformations during the late stages of syntheses involving complicated substrates, and cascade reactions that significantly increase molecular complexity.

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1 Introduction

The study of small-molecule natural products during the past century has delivered enormous amounts of knowledge, and this knowledge has had a significant impact on the shape of organic chemistry and biomedical research, with total synthesis playing an important role in both of these areas. For a large number of complex natural products, the unique structural features, including their fascinating polycyclic skeletons and rich stereochemical components in particular, have not only challenged generation after generation of synthetic chemists, but have also served as sources of inspiration for method development. It is undeniable that the transition-metal-catalyzed reactions have had a massive impact on the organic synthesis of natural products, where they have been frequently used to affect key transformations for the construction of multiple chemical bonds. Within the expanding territory of transition metal organometallic chemistry, there has been a noticeable trend during the past decade towards the use of homogeneous gold-catalyzed transformations, and the potential of these transformations has been exemplified in a number of total syntheses.[1–22]

Elemental gold has an atomic number of 79 and an electron configuration of $[Xe]4f^{14}5d^{10}6s^{1}$. The relativistic effects underline the contracted 6s orbital and expanded 5d orbitals of gold, endowing cationic gold complexes with superior π-acidity and the ability to stabilize adjacent carbocations by back-donation.[23] The high oxidation potential of Au(I) to Au(III), which is also related to the relativistic effects, explains why reactions involving oxidative addition and reductive elimination process on gold catalysts are rarely reported. Although this field is undergoing dramatic changes and reactions involving the Au^{I}/

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Au^{III} catalytic cycle are being reported with increasing frequency,[24–34] this review will focus primarily on gold(I)-catalyzed transformations. Structurally, Au(I) predominantly forms linear two-coordinate complexes, and the abstraction of a coordinating halide is therefore generally required to provide a free coordination position on the Au(I) center for incoming ligands. The "soft" Lewis acidity of large cationic Au(I) ions that share the positive charge with their ligand results in a preference for them binding to "soft" Lewis bases, such as the π-systems, rather than oxygen (a "hard" Lewis base). Consequently, the high air and moisture stability of gold catalysts adds to their practical value in terms of their application in organic synthesis. Furthermore, the outer-sphere mechanism of a gold(I)-catalyzed reaction involves the *anti*-addition of the nucleophile to the activated π-system with respect to gold. It has been shown that the reactivity of gold catalysts, as well as the outcome of their reactions, can be fine-tuned with different ligands and counterions.[35]

Several excellent reviews on the use of gold catalysis in total synthesis have been published in the literature.[4,5] The ability of homogeneous gold catalysis to construct complex ring systems, which are crucial for natural product synthesis, was first shown by Hashmi and co-workers in 2000.[36,37] This was followed by a number of elegant methodologies in 2004, including the Conia-ene reaction of β-ketoesters and the diastereoselective 3,3-rearrangements developed by Toste *et al.*,[38,39] the enyne cyclization reactions developed by Echavarren *et al.*,[40] and the enyne cycloisomerization process developed by Zhang and Kozmin,[41] which fuelled an explosion of interest in expanding the structural motifs accessible to gold catalysis.[42] Although a comprehensive review of gold catalysis is beyond the scope of this review, we herein report the power and potential opportunities associated with the use of gold catalysis in the total synthesis of complex molecules by highlighting cases where the chemo- and regio-selective gold-catalyzed reactions have been used to efficiently construct the unique structural features of complex natural products. This review has been organized based on the structural characteristics of the target molecules, with sections devoted exclusively to the use of gold-catalyzed reactions for the construction of terpenoids, polyketides and alkaloids.

2 Terpenoids

2.1 Cyclization and pericyclic reactions

Gomerone C (**1**, Scheme 1) is a sesquiterpene, which was isolated from samples of *Laurencia majuscula* collected from the southern coast of La Gomera, Canary Islands. As a member of the halogenated terpenoids, which possess a range of interesting biological activities, gomerone C consists of an interesting and challenging skeleton that invites structural and synthetic studies. It is noteworthy that the structure of gomerone C was originally assigned as compound **2**, bearing a tricyclic carbon skeleton with two contiguous quaternary centers at C6 and C11. This structure was further rigidified by the presence of an unusual bicycle [3.2.1]octane containing two chloride-substituted carbons with one chloride positioned at the bridgehead. The total synthesis of gomerone C by Carreira *et al.*,[43] however, led to its structure being revised to **1**, which is the C3 diastereomer of **2**. Under the governance of Bredt's rule, the impossibility of installing a chloride at the bridgehead

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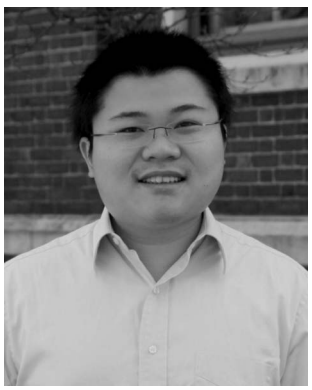
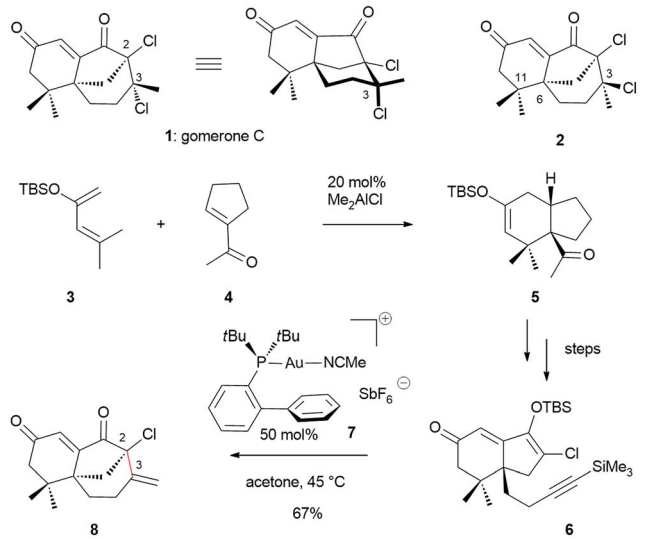


Tuoping Luo won a Gold Medal in the 33rd International Chemistry Olympiad (IChO) during high school. In 2005, he received a BS in chemistry from Peking University. He received his Ph.D. degree with Professor Stuart L. Schreiber at Harvard University and Broad Institute. He did his post-doctorate research in H3 Biomedicine Inc., a start-up company focusing on oncology drug development. He returned to Peking University in 2013 and started his independent group, which concentrates on the development of biologically active small molecules.

Zhen Yang studied medicinal chemistry at Shenyang College of Pharmacy and earned a PhD at The Chinese University of Hong Kong in 1992 under the guidance of H. N. C. Wong. He carried out postdoctoral research on natural-product synthesis with K. C. Nicolaou at The Scripps Research Institute in La Jolla, CA, and joined its faculty in 1995. In 1998, he moved to the Institute of Chemistry and Cell Biology of Harvard Medical School as an institute fellow before returning to China as a professor at Peking University in 2001. His research is devoted to the total synthesis of natural products and chemical biology.

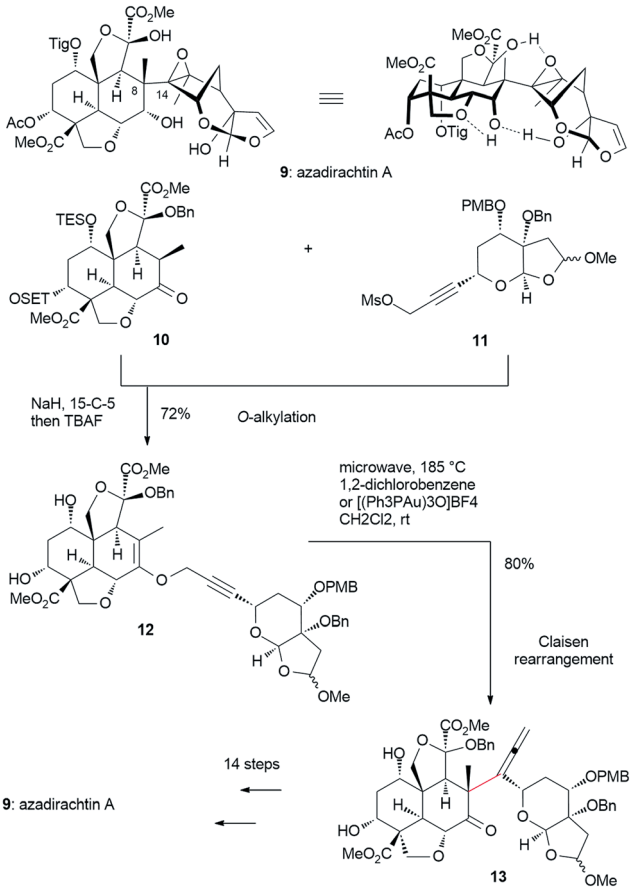


Scheme 1 The total synthesis of gomerone C.

through enolate chemistry led to significant developments in the capability of a late-stage Conia-ene reaction to allow for the construction of the tricyclic scaffold bearing an exocyclic olefin from an α-chlorinated silyl enol ether and an alkyne. This total synthesis commenced with the preparation of the Diels–Alder adduct **5** featuring the fused 5,6-bicyclic scaffold with two adjacent quaternary centers from silyloxydiene **3** and enone **4**. The source of the Conia-ene precursor was successfully reconciled by converting **5** to the chlorinated silyl enol ether **6** *via* sequential oxidation and carbon elongation reactions. The treatment of **6** with acetonitrile [(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoro- antimonate (**7**, Echavarren's catalyst) not only initiated the nucleophilic stage of the Conia-ene reaction, leading to tricyclic product **6** with the desired quaternary carbon center, but also accomplished the concomitant removal of the silyl protecting group on the alkyne in one step (the resulting carbon–carbon bond has been highlighted in red in the scheme). The subsequent addition of hydrogen chloride to the exocyclic olefin in **8** under the optimized conditions afforded gomerone C (**1**), and its structure was confirmed by single crystal X-ray analysis.

The synthetic prowess of the gold-catalyzed Conia-ene reaction was first alluded to and applied in the pioneering synthesis of (+)-fawcettimine, which was reported by Toste *et al.* (*vide infra*).[44] In a similar vein, the use of Echavarren's catalyst in conjunction with a Buchwald-type ligand for the synthesis of gomerone C facilitated the regioselective 6-*exo*-dig cyclization in 65% yield. In this particular case, the cyclization of the enolate carbon nucleophiles to gold-coordinated alkynes provides a good illustration of the role of the gold catalyst in total synthesis.

Azadirachtin A (**9**, Scheme 2) was isolated from the Indian neem tree *Azadirachta indica* in 1968, and is representative of the azadirachtin/meliacarpin-class of natural products, which are a series of highly oxygenated limonoids with a variety of different biological activities, including potent antifeedant



Scheme 2 The total synthesis of azadirachtin A.

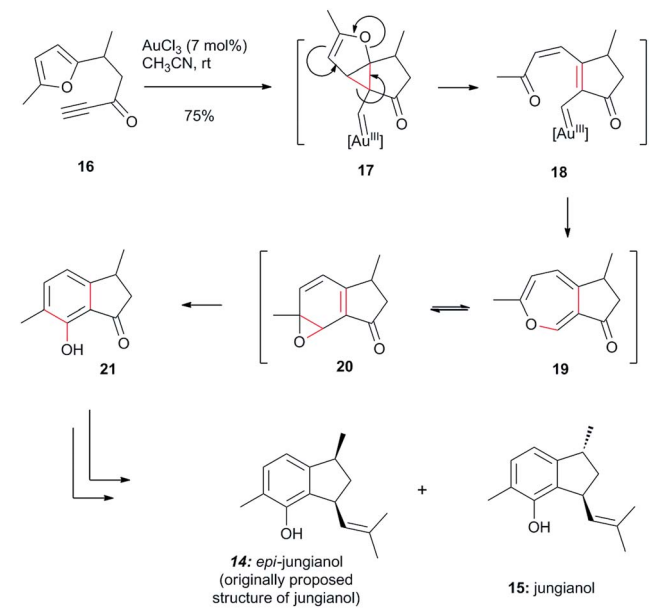
activity.[45] Ley *et al.*[46] successfully achieved the "relay total synthesis" of azadirachtin A in 2007, after overcoming a series of complex synthetic challenges, and this work represents the only successful chemical synthesis of an azadirachtin reported to date. A cursory inspection of the complex molecular architecture of this compound reveals 16 contiguous stereogenic centers, including seven quaternary centers, and eight rings, including an epoxide. The most challenging aspect of this molecule from a synthetic perspective is that the highly oxygenated azadirachtin A is sensitive to acid and base as well as light, making it prone to rearrangement reactions, and these issues have frustrated a great many synthetic plans. In response to the failure of a number of strategies aimed at directly installing the C8–C14 linkage, Ley *et al.* developed a new synthetic route that proceeded *via* the Claisen rearrangement of propargylic enol ether **12**. This rearrangement could be affected under thermal conditions or catalytic conditions in the presence of a cationic gold catalyst. With these objectives in mind, the requisite decalin and pyran fragments **10** and **11** were coupled together by a selective *O*-alkylation process, which enabled a high level of convergence and minimized steric crowding during the fragment coupling process. The Claisen rearrangement of propargylic enol ether **12** was achieved by microwave heating at 185 °C to afford allene **13**, which was subjected to a series of further steps to give the target molecule.

The Claisen rearrangement could also be successfully conducted in the presence of $[(Ph_3PAu)_3O]BF_4$ at room temperature to give **13** in 80% yield. Mechanistically, the 6-*endo*-dig addition of the enol ether to the gold(I)-alkyne complex would lead to the formation of an intermediate that would undergo Grob-type fragmentation to give the β-allenic aldehyde together with the regenerated cationic Au(I) catalyst. Even though gold catalyzed propargyl Claisen rearrangements involving an electrophilic Au(I)-oxo species had already been reported in the literature,[39] the successful implementation of this transformation in such an oxygen-rich and highly complex substrate (**12**) with high levels of chemo-, regio-, and diastereoselectivity represents a remarkable achievement, and provides a good demonstration of the robust nature of this gold-catalyzed transformation.

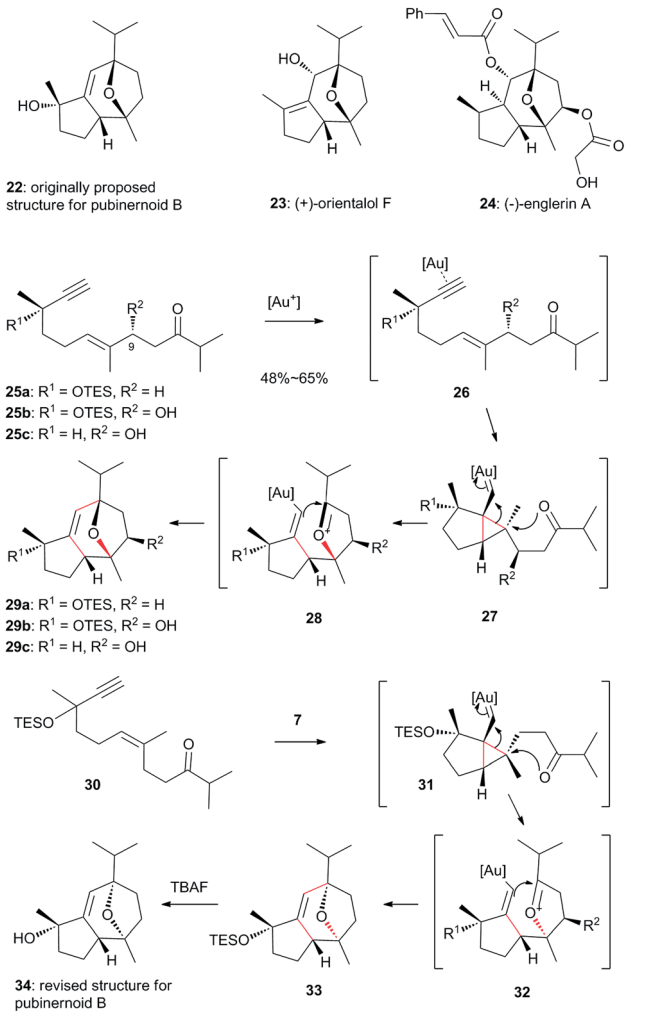
2.2 Cascade reactions for the construction of multiple chemical bonds

Jungianol (**15**, Scheme 3). which is a sesquiterpene isolated from *Jungia malvaefolia* that was first characterized by Bohlmann *et al.*[47] in 1977, was successfully synthesized according to a protecting-group-free process using a method developed by Hashmi *et al.*[36,37] for the gold-catalyzed synthesis of phenols bearing a phenolic hydroxyl group *ortho*- to the ring-junction. The cascade began with the cyclization of the furan ring to the gold-coordinated triple bond in ketone **16** to give the cyclopropyl carbenoid intermediate **17**, which rearranged to give carbenoid **18**.[48] Subsequent nucleophilic attack of the carbonyl oxygen atom and elimination of gold provided the oxepine intermediate **19** and its arene oxide tautomer **20**, which underwent a regioselective epoxide ring opening followed by aromatization at room temperature to afford phenol **21** in 75% yield.[49] The mechanism of a similar gold-catalyzed cycloisomerization reaction was supported by *in situ* NMR analysis of the trapped intermediates.[50,51] Jungianol **15** and *epi*-jungianol **14** were synthesized in two steps from **21**, with the benzoid arene scaffold fused to a five-membered ring.

One of the most remarkable applications of the gold-catalyzed enyne cyclization in natural product synthesis was reported by Echavarren *et al.*[52,53] in their work towards the development of a general strategy for the synthesis of sesquiterpenoids, including pubinernoid B (originally assigned as **22**, revised to **34**, Scheme 4), orientalol F (**23**), and englerin A (**24**). All three of these natural products share an oxatricyclic skeleton that would be amenable to the gold-catalyzed formal [2 + 2 + 2] alkyne/alkene/carbonyl cycloaddition developed by Echavarren *et al.*[54] The preponderance of gold(I)-catalyzed stereospecific reactions of 1,5-enynes to reveal [3.1.0] bicyclic structures provided the inspiration for this polycyclization reaction through the further trapping of the cyclopropyl metal carbene with a suitable nucleophile. In this particular case, the use of ketoenynes **25a**, **25b** and **30** bearing a propargylic alcohol motif allowed for the construction of late-stage intermediates **29a**, **29b** and **33** in a single step, with only minor functional group manipulations being required to complete the total syntheses.



Scheme 3 The total synthesis of jungianol and *epi*-jungianol.



Scheme 4 Total syntheses of pubinernoid B, orientalol F and englerin A.

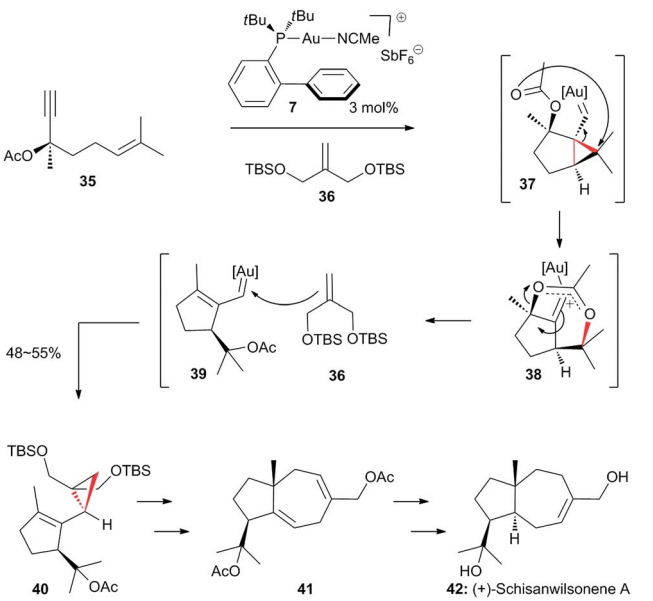
However, the domino reaction providing access to the oxatricyclic core could have been thwarted by the propargylic oxygen substituents for several reasons, including (1) propargylic alcohols are prone to undergoing the Meyer–Schuster rearrangement or nucleophilic attack in the presence of the gold catalysts; (2) propargylic carboxylates readily undergo metal-catalyzed 1,2- or 1,3-acyl migrations;[55–57] and (3) propargyl alcohols, ethers, and silyl ethers may undergo the gold(I)-catalyzed intramolecular 1,5-migration of their OR groups to give the corresponding products,[58] which are useful intermediates in the synthesis of (+)-schisanwilsonene A (*vide infra*).

Furthermore, the rearrangement of enynes to dienes has already been well established in 1,6-enyne substrates,[59] and represents nothing more than another side reaction. Despite these potential issues, extensive experimental work led to the identification of optimum conditions for the conversion of racemic **35a** to racemic **29a** in 65% yield, with the configuration of the product being confirmed by X-ray crystallographic analysis of a closely related derivative. An important discovery in this gold-catalyzed cascade reaction of propargylic-functionalized ketoenynes was that the cyclization proceeded exclusively through intermediate **27**, where the OTES group and the gold carbene were *anti*-oriented.

Analysis of the ^{1}H NMR data for compound **23**, which was obtained *via* the elaboration of **29a**, revealed that the data were not in agreement with those reported for pubinernoid B, and this disparity led the authors to prepare ketoenyne substrate **30** bearing a *Z* olefin. Once again, the stereoselectivity of the gold-catalyzed domino reaction was dictated by the propargylic OTES in the presence of catalyst **7**, presumably *via* intermediate **31**. Ultimately, (±)-**34** was afforded in modest yield following desilylation. The NMR data for **34** were identical to those reported for pubinernoid B, and the structure of the natural product was revised accordingly. The synthesis of (+)-orientalol F (**23**) was achieved *via* the gold-catalyzed domino reaction of (*S*)-**25a**, which gave enantioenriched **29a** without racemization. This compound was then converted to the target molecule in only three steps.

Englerin A (**24**) is a guaiane sesquiterpene isolated from *Phyllanthus engleri* that exhibits potent inhibitory activity towards the growth of renal cancer cells, with GI_{50} values in the range of 1–87 nM. A recent investigation of the mechanism-of-action of englerin A demonstrated that it can selectively bind to and activate protein kinase C-θ (PKCθ) and thereby limit the access of tumor cells to glucose.[60] In light of its promising anticancer activities, englerin A has been the subject of considerable synthetic interest from various groups, with a number of total syntheses and a formal synthesis being reported.[52,61–66] Echavarren *et al.*[52] reported the total synthesis englerin A *via* the chiral linear chain compound **25b**, which was used to form the oxatricyclo framework in **29b** *via* a gold-catalyzed formal [2 + 2 + 2] cycloaddition that allowed for the simultaneous formation of two C–C bonds and one C–O bond. Ma *et al.*[63] independently reported the synthesis of englerin A from the enantiopure ketoenyne, which afforded **29c**. Considering that the C9 hydroxyl substituent could interfere with the ring opening of the carbonyl group and lead to the premature termination of the domino process, the efficient performance of the domino cyclization process in the presence of an unprotected alcohol group at the stereogenic allylic position was particularly remarkable. The late-stage intermediates **29b** and **29c** were subsequently converted to (−)-englerin A (**24**) in 9 and 10 steps, respectively. In a later publication, Echavarren *et al.*[67] reported the first total synthesis of (+)-schisanwilsonene A (**42**, Scheme 5) based on their newly developed gold(I)-catalyzed tandem reaction of 1,6-enynes.

(+)-Schisanwilsonene A (**42**) is a carotene-type sesquiterpenoid derived from *Schisandra wilsoniana*, and the fruits of this medicinal plant have been used in traditional Chinese medicine for the treatment of hepatitis. Furthermore, this compound shows antiviral activity, inhibiting HBsAg and HBeAg at a concentration of 50 μg mL^{-1}.[68] The enantioenriched substrate 1,6-enyne **35** (96 : 4 e.r.) bearing a propargylic acetate group underwent a gold(I)-catalyzed cyclopropanation reaction in the presence of catalyst **7** followed by the intramolecular transfer of the acetate carbonyl group through intermediates **37** and **38** to give the unsaturated gold-carbenoid **39**. Subsequent cyclopropanation of alkene **36** with **39** afforded **40** in 48–55% yield with an e.r. of 91 : 9. Given that the cyclization of propargyl acetates provides a competitive and facile process through which substrates can undergo gold(I)-promoted 1,2- or 1,3-migrations or other cycloisomerization pathways, the successful cascade cyclization/1,5-migration/cyclopropanation of **35** to give **40** as the final product represents a remarkable transformation. It has been suggested that the major 1,6-enyne cyclization pathway, which was triggered by the gold activated η^2-alkyne being attacked intramolecularly by an alkene, was faster than the competing 1,2-acyl migration. With **40** in hand, the bicyclic diene **41** was prepared in four steps *via* the [3,3]-sigmatropic rearrangement of a divinyl cyclopropane intermediate, which allowed for the enantioselective synthesis of **42** to be completed in seven more steps.

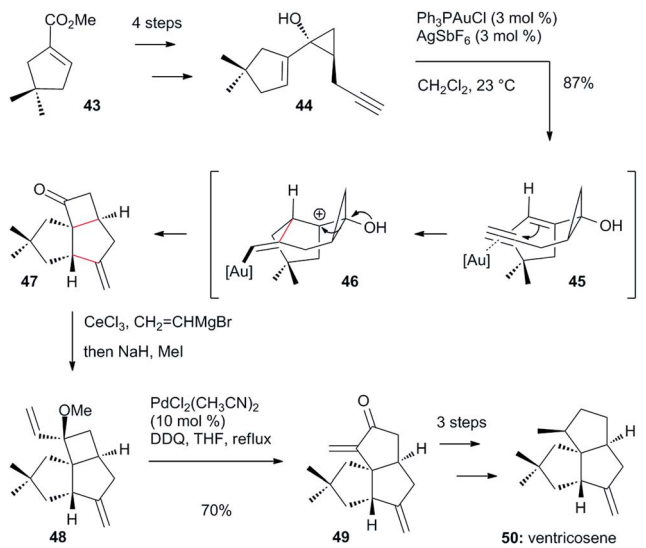


Scheme 5 The total synthesis of (+)-schisanwilsonene A.

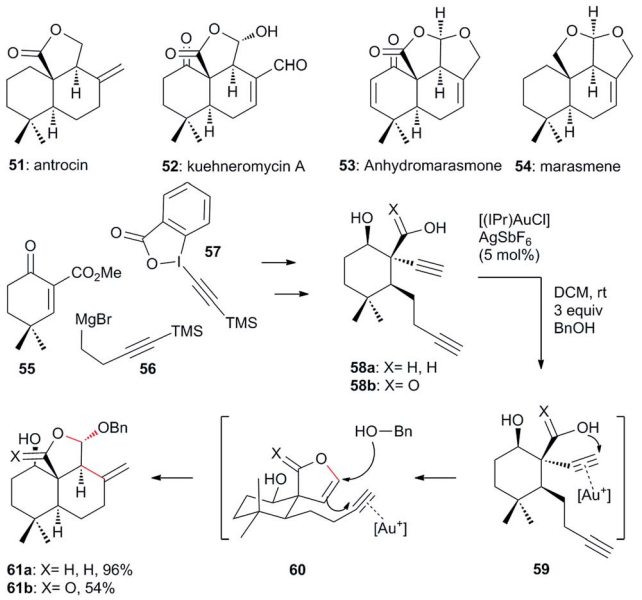
As shown above, gold-catalyzed enyne cycloisomerization reactions have had a significant impact on the synthesis of polycyclic ring systems, where the gold-carbenoids or carbocation intermediates induce skeletal rearrangement processes that are driven by the release of ring strain. The enyne cycloisomerization/ring expansion tandem reaction reported by Toste *et al.*[69] in their synthesis of ventricosene (**50**, Scheme 6) provides another good example of this process.

In this case, the synthesis began with the preparation of enyne **44** from the commercially available ester **43**. In an exquisite sequence of cycloisomerization events, the attack of the gold(I)-coordinated alkyne in **45** by the alkene gave carbocation **46**, which underwent a semipinacol rearrangement to give the cyclobutanone product **47** in 87% isolated yield as a single diastereomer. The selectivity of this gold-catalyzed cycloisomerization was particularly impressive, with the required angular triquinane ring bearing a methyl chiral center remaining intact. The high level of selectivity observed in this reaction was attributed to the fact that (1) the semipinacol shift leading to the high-energy *trans*-cyclobutanones could not occur; and (2) the transition state resembling a high-energy *trans*-diquinane conformation would be avoided. The gold-catalyzed cascade reaction product **47** was subsequently converted to **48**, which underwent a palladium(II)-catalyzed oxidative ring expansion followed by three additional steps to complete the 11-step racemic synthesis of ventricosene **50**. Although Cha *et al.*[70] developed a similar reaction involving the cyclization of 1-vinylcyclopropanol to a tethered aldehyde instead of an alkyne, Toste's application of this gold-catalyzed cascade reaction for the construction of a tricyclic ring system represents an efficient and atom-economical approach for accessing various angular triquinanes, as well as minimizing the tedious functional group manipulation processes required of conventional synthetic approaches.

Inspired and motivated by these masterpieces, we became interested in drimane-type sesquiterpenoids that were



Scheme 6 The total synthesis of ventricosene.



Scheme 7 The total synthesis of drimane-type sesquiterpenoids.

oxygenated at C-15, such as antrocin (**51**, Scheme 7), kuehneromycin A (**52**), anhydromarasmone (**53**) and marasmene (**54**), which all share a 5,6,6-tricyclic scaffold that could be constructed *via* a gold-catalyzed tandem process.

Conventional synthetic strategies towards these sesquiterpenoids general involve the use of an intramolecular Diels–Alder reaction for the construction of the tricyclic core structure.[71–76] It was envisaged, however, that the novel gold-catalyzed cascade reaction of 1,7-diynes would provide a unique and flexible approach to these skeletons.[77] With this in mind, we assembled racemic 1,7-diynes **58a** and **58b** from readily available starting materials **55**, **56** and **57**. The key transformation was initiated by the 5-*endo*-dig addition of oxygen to the first alkyne (**59**), leading to the polarized olefin functionality in **60**, which functioned as a nucleophile in the subsequent 6-*exo*-dig cyclization, following the activation of the other alkyne. The reaction was then terminated by the addition of an external nucleophile (*i.e.*, benzylic alcohol in this case). Under the optimized conditions, the gold-catalyzed cascade reactions of **58a** and **58b** afforded the desired products **61a** and **61b** in 96 and 54% yields, respectively. Subsequent functional group manipulations allowed for the efficient conversion of **61a** and **61b** to the natural products **51**, **52**, **53** and **54**. Thus a unified strategy was developed for the synthesis of the aforementioned drimane-type sesquiterpenoids based on an enabling gold-catalyzed cascade reaction, and the high chemo-, regio- (*e.g.*, primary *versus* secondary alcohol) and diastereoselectivity of this transformation effectively emphasized its practicality for the construction of polycyclic scaffolds.

3 Polyketides

3.1 Cyclization leading to five-membered furan ring systems

Polyketides are a structurally diverse family of natural products with important biological activities and pharmacological

properties. The application of the gold-catalyzed hydrofunctionalization process to these systems would provide flexible and efficient access to furan and pyran ring systems, which are ubiquitous skeletal motifs in polyketide natural products.

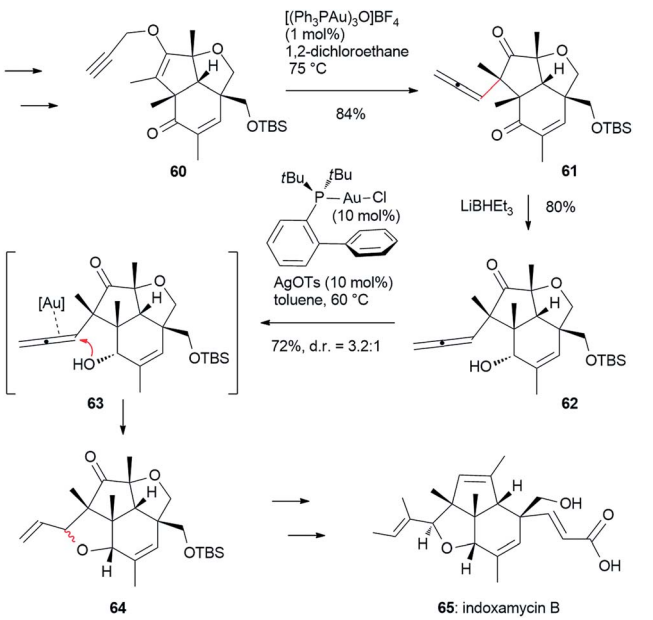
The power and utility of the gold-catalyzed reaction in this context is exemplified by the total synthesis of indoxamycin B (**67**, Scheme 8), which is a member of the novel indoxamycin class of marine natural products, by Carreira *et al.*[78] Consideration of the target molecule reveals six contiguous stereocenters, two of which are quaternary, across a 5,5,6-tricyclic skeleton. This is an area where rearrangement reactions often prove their worth. The salient features of the key gold-catalyzed transformations include a Saucy–Marbet rearrangement (*i.e.*, propargyl Claisen rearrangement as discuss in the total synthesis of azadirachtin A, *vide supra*) and an intramolecular allene hydroalkoxylation, which allowed for the successful construction of a highly substituted tetrahydrofuran ring within the target molecule. Thus, propargyl vinyl ether **62** was subjected to the trinuclear Au(I)-oxo complex $[(Ph_3PAu)_3O]BF_4$ catalyst (1 mol%) to give allene **63** with the correct quaternary stereocenter. Following the reduction of the cyclohexenone carbonyl group to the corresponding hydroxyl group, the resulting allene **64** underwent the *exo*-hydroalkoxylation in the presence of the cationic gold catalyst (10 mol%) and the sterically hindered ligand 2-(di-*tert*-butylphosphino)-biphenyl[79] to afford tetracyclic intermediate **66** as a mixture of inseparable diastereomers at C2 in 72% yield. Further elaboration of **66** gave indoxamycin B (**67**), which not only realized the first synthesis of a member of this unprecedented structural class but also resulted in the stereochemical reassignment of the natural product.

3.2 Cyclization leading to six-membered pyran ring systems

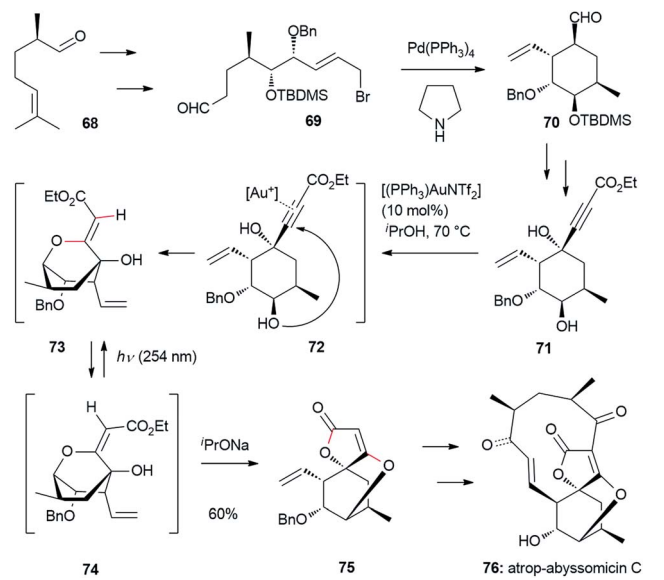
Bihelovic and Saicic made use of a gold-catalyzed tandem reaction for a one-pot spirotetronate formation in their synthesis of (−)-atrop-abyssomicin C (**76**, Scheme 9), which is a secondary metabolite with the highest bactericidal bioactivity of its known congeners.[80]

The total synthesis of this molecule has previously been accomplished by the groups of Sorensen and Nicolaou, who both used a Diels–Alder reaction to construct the cyclohexane ring system, as well as an intramolecular epoxide ring opening process to form the oxygen bridge.[81–83] In contrast, Bihelovic and Saicic developed an alternative enantioselective route based on dual catalysis for the formation of the cyclohexane core with all of the stereocenters installed, a gold-catalyzed cascade reaction for the formation of the spirotetronate, and a Nozaki–Hiyama–Kishi reaction for the formation of the 11-membered ring. Their synthesis commenced with the conversion of (−)-(*R*)-norcitronellal **68** to aldehyde **69**, which underwent a Pd-catalyzed Tsuji–Trost cyclization to give cyclohexane **70**, bearing five contiguous stereocenters. Alkyne **71**, the substrate for the gold-catalyzed reaction, was obtained in four steps from aldehyde **70**, and treated with Gagosz's gold catalyst $[(PPh)_3AuNTf_2]$ to afford the bridged bicycle **73** *via* the nucleophilic addition of the hydroxyl group (*cf.* **72**). It was necessary, however, for the *Z*-configured olefin **73** to be isomerized to the *E* isomer **74** to allow for the formation of the desired tricyclic tetronate **75**, and this process was effected in one-pot by the irradiation of **73** with UV light in the presence of a catalytic amount of sodium isopropoxide. The key intermediate **75** was taken forward to complete the total synthesis of (−)-atrop-abyssomicin C (**76**) in eight transformations, with the 11-membered ring being efficiently closed by the intramolecular Nozaki–Hiyama–Kishi reaction. Thus, the use of the gold-catalyzed cascade reaction together with irradiation resulted in the facile construction of the tricyclic core **75** from the monocyclic starting material **71**.

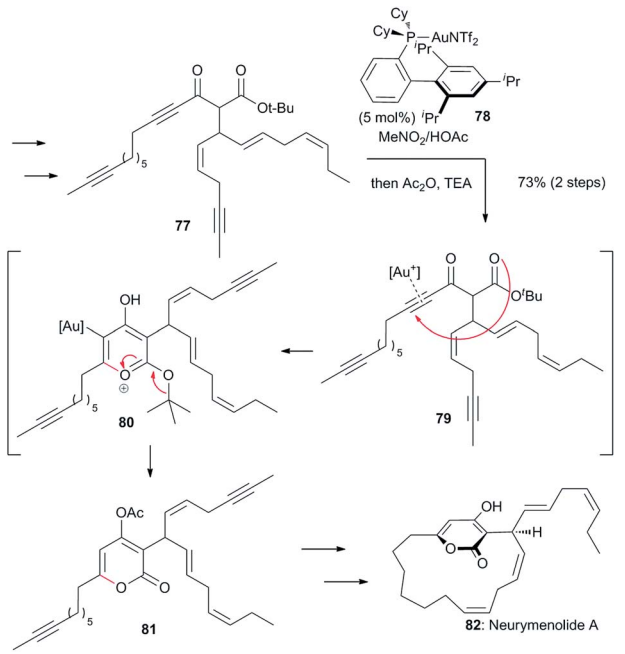
Neurymenolide A (**82**, Scheme 10), which is an α-pyrone-derived natural product that exhibits appreciable activity against methicillin-resistant *Staphylococcus aureus* and



Scheme 8 The total synthesis of indoxamycin B.



Scheme 9 The total synthesis of (−)-atrop-abyssomicin C.



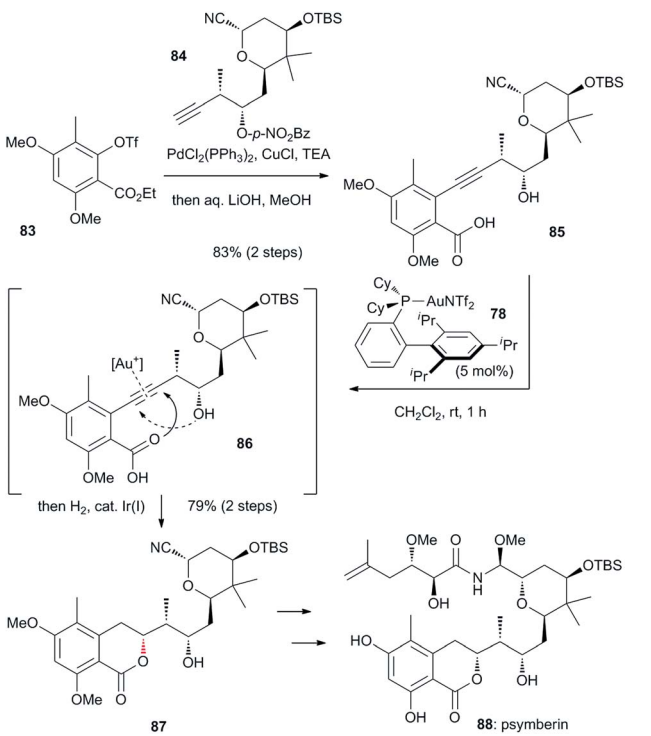
Scheme 10 The total synthesis of neurymenolide A.

vancomycin-resistant *Enterococcus faecium*,[84] was synthesized by Fürstner *et al.*[85] *via* a gold-catalyzed cyclization, and represents the only total synthesis of this compound to have been reported to date.

The unusual carbon skeleton of neurymenolide A makes it exceptionally labile because it contains a skipped array of four double bonds, two of which could migrate into conjugation with the pyrone ring. It was envisaged in a concise synthetic strategy that the pivotal 4-hydroxy-2-pyrone could be synthesized *via* the heteroannulation reaction of the highly sensitive enyne 77, which contained six different non-conjugated unsaturated bonds, because the resulting pyrone could potentially impart some stability to the labile polyunsaturated system. Although in practice this transformation was plagued by numerous competing side reactions and decomposition pathways, pleasingly, following a period of optimization, the use of the bulky Xphos-ligated gold complex **78** as a catalyst at room temperature with HOAc as a co-solvent gave α-pyrone **80** after acetylation. Mechanistically, it was proposed that the activation of the alkyne with the gold-catalyst (*cf.* **79**) would have provided the cationic pyrone intermediate **80**. Subsequent cleavage of the *tert*-butyl group would have allowed for the release of the pyrone ring, with the critical proto-deauration step being strongly facilitated by the use of HOAc as a co-solvent. Detailed consideration of substrate 77 revealed that the alkyne conjugated to the keto group had the lowest affinity of the three alkynes for the cationic gold species because it possessed the least electron density, and one potential competing side reaction would be the gold-catalyzed 6-*exo-dig* Conia-ene cyclization. It was therefore satisfying that the desired product **81** was obtained in good isolated yield (73%), even though the *in situ* acetylation of the resulting 4-hydroxyl-2- pyrone was essential to suppress the rapid isomerization of the lateral alkenes.

The utility of the gold-catalyzed cyclization was nicely illustrated by Brabander *et al.*[86] in 2012 in their second generation synthesis of psymberin (**88**, Scheme 11).

Interestingly, the same group developed their first total synthesis of this target molecule in 2005.[87] Over the past few years, a number of reports have appeared in the literature describing the total synthesis[88–93] of psymberin, and some formal,[94] fragment[95–103] and analog syntheses[104–106] of this natural product have also been reported. In contrast to other members of the pederin family,[107–110] psymberin is uniquely extended with a dihydroisocoumarin unit lacking an acetal-containing pederate side chain, and displays a highly differential cytotoxicity profile, suggesting that it operates *via* an alternative mode of action to its other family members. Noting that the dihydroisocoumarin fragment could provide opportunities for SAR studies around the aromatic fragment, the team reasoned that the complex molecular framework of psymberin could be retrosynthetically reduced to the alkyne-substituted benzoic acid derivative **85**, which could be readily prepared from triflate **83** (a versatile building block) in a Sonogashira cross-coupling reaction. However, the key 6-*endo*-dig cyclization of carboxylic acid **85** following the activation of the alkyne would compete with the 5-*exo*-dig cyclization of the carboxylic acid and the 5-*endo*-dig cyclization of the homopropargylic alcohol motif (*cf.* the dotted arrow in **86**). This problem was solved by extensive optimization experiments that identified suitable conditions involving Gagosz's catalyst and Xphos-ligated $AuNTf_2$, which gave rise to the desired isocoumarin in 79% yield at ambient temperature. Subsequent hydrogenation in the presence of Crabtree's catalyst provided



Scheme 11 The total synthesis of psymberin.

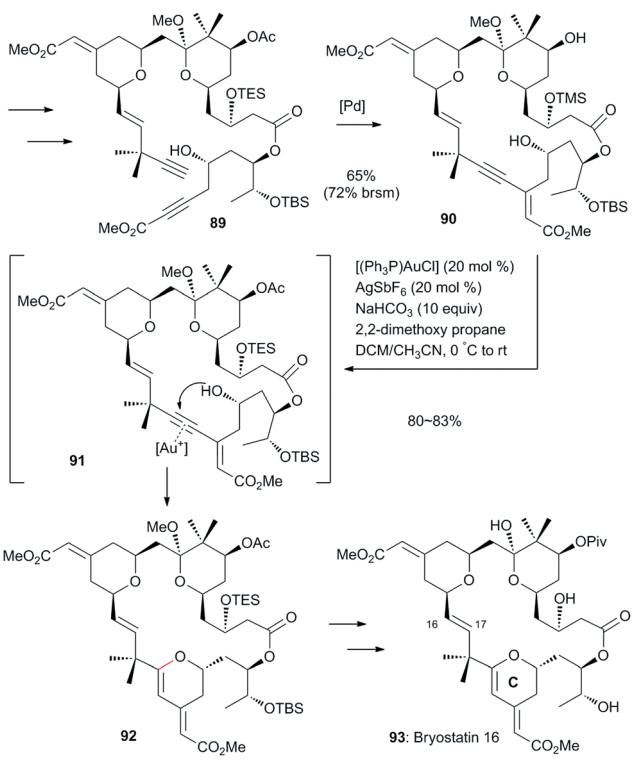
dihydroisocoumarin **87** in quantitative yield, with only a few more steps required to give psymberin (**88**). Thus, as highlighted in this case, the gold-catalyzed chemo- and regioselective isocoumarin formation allowed for the construction of the desired C–O bond from an *ortho*-alkynyl benzoic acid with the unprotected hydroxyl group remaining intact. This strategy therefore allowed for the late stage introduction of the aromatic fragment to the target molecule and a solution to the extensive protecting group issues reported in the previous synthesis.

As a matter of fact, the total synthesis of macrolactone bryostatin 16 (**93**, Scheme 12) in 2008 by the Trost group pioneered a late-stage gold-catalyzed dihydropyran formation, and embodied the philosophy of atom-economy through the development of synthetically useful techniques.[111,112] Bryostatin compounds showing promising anti-cancer activities have several structural features in common, including a 26-membered macrolactone containing three embedded and highly functionalized pyran rings, as well as two *exo*-cyclic unsaturated esters and one congested C16–C17 *trans*-olefin, and these features have resulted in the failure of several routes relying on metathesis-based strategies. For their construction of the C-ring of bryostatin 16 (**93**), Trost and Dong initially used a palladium-catalyzed alkyne-alkyne coupling macrocyclization to afford macrolide **90**. Exposure of **90** to a cationic gold(I) catalyst in the presence of $NaHCO_3$ at ambient temperature led to the rapid formation of the acid-sensitive 6-*endo*-dig cyclization product dihydropyran **92** in 80–83% yield, which was subsequently elaborated to target molecule **93** in two steps. The use of a gold-catalyzed nucleophilic cyclization was critical for the successful formation of the six-membered pyran ring over the five-membered furan product. The use of a palladium catalyst gave inseparable mixtures of the 5-*exo*-dig and 6-*endo*-dig cyclization products.

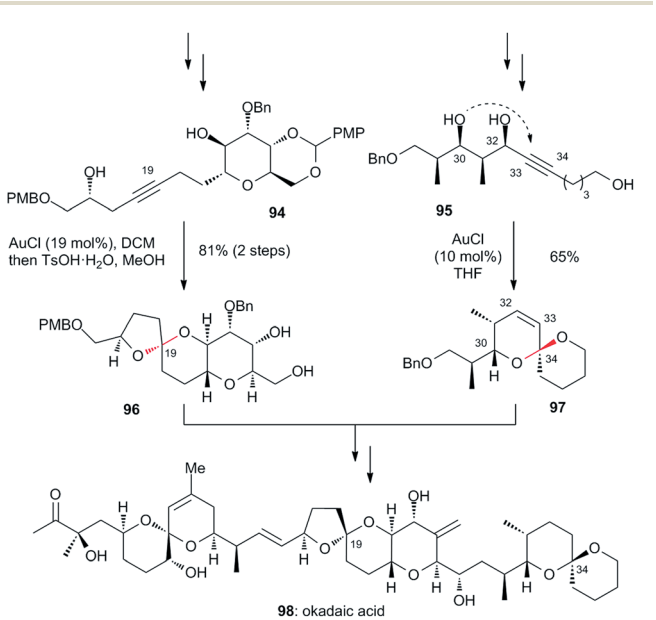
3.3 Gold-catalyzed reactions in spiroketal synthesis

The gold-catalyzed spiroketalization reaction represents a powerful method for the synthesis of a broad range of spiroketal-containing natural products.

One prominent example involves the dual use of a regiocontrolled gold-catalyzed spiroketalization by Forsyth *et al.*[113] in their formal total synthesis of okadaic acid (**98**, Scheme 13). Okadaic acid (**98**) contains three spiroketal motifs and is a potent protein serine-threonine phosphatase inhibitor that has been widely used as a small-molecule probe in biological studies.[114] Forsyth *et al.*[115,116] have conducted several studies towards the synthesis of this formidable polyether natural product and its analogs. In their most recent fragment synthesis, the C19 spiroketal was derived from the reaction of alkyne **94** with a catalytic amount of AuCl in CH_2Cl_2 followed by the addition of TsOH in methanol, which completely removed the anisylidene group to give diol **96** as the final product in 81% yield. The formation of the latter C34 spiroketal (**97**) was likely initiated by a regioselective cyclization, which would have been influenced by the relative 1,3-stereochemistry of the propargylic and nucleophilic hydroxyls within triol **95**, because only the 1,3-*anti* triol gave the desired 1,7-dioxaspiro[5.5]-undecane system exclusively. Thus, compound **95** suitably evaded the hindered oxy-auration of the alkyne *via* 5-*exo* addition at C33 (*cf.* the dotted arrow in **95**) and proceeded *via* the less sterically encumbered 6-*exo* oxy-auration. The resulting α-hydroxy vinyl gold species then underwent the concerted loss of gold hydroxide followed by the isomerization of the exocyclic allenyl ether to give a vinyl substituted oxocarbenium ion, which was



Scheme 12 The total synthesis of bryostatin 16.



Scheme 13 The formal synthesis of okadaic acid.

attacked by the C30 hydroxyl to afford **97**. The use of an alkyne as a dehydrated surrogate for a ketone avoided potential sensitivity problems relating to the highly functionalized ketones, whereas the acid sensitive substrates **96** and **97** were well tolerated under the mild conditions required of the gold-catalyzed reactions. This spectacular example also clearly illustrates the subtlety of the gold-catalyzed regiocontrolled spiroketalization.

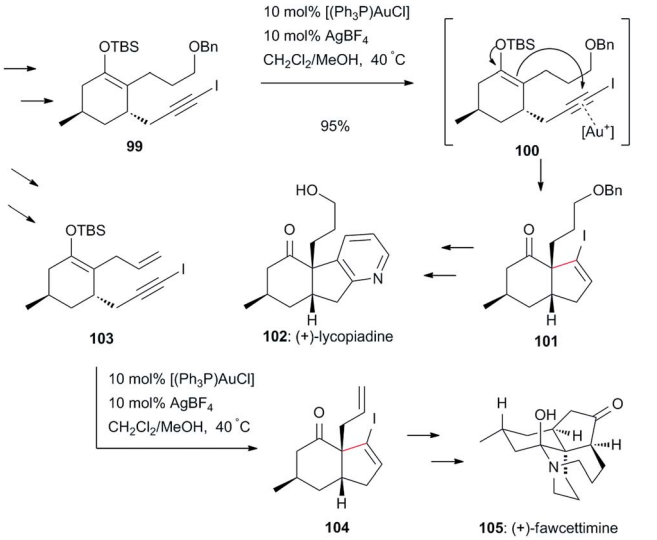
Other cases of gold-catalyzed spiroketalization include the stereoselective synthesis of the 5,5-spiroketal unit within the epimeric cephalosporolide H isomers by Dudley *et al.*,[117,118] as well as the preparation of a 6,6-spiroketal fragment in the total synthesis of (−)-ushikulide A by Trost *et al.*[119] Spiroketals can also be prepared in a stepwise fashion using a gold catalyst, such as the preparation of the 5,5-spiroketal in (+)-cephalostatin 1 by Shair *et al.*,[120] and the preparation of the 6,6-spiroketal motif in the second-generation synthesis of spirastrellolide F methyl ester reported by Fürstner *et al.*[121] The gold-catalyzed reaction represents an extraordinary method for the formation of carbon–oxygen bonds in both a single step and a cascade reaction to furnish the desired ring systems, and yet chemistry appears to only be at the beginning of tapping the true potential of the chemo-, regio- and stereoselectivity of this process. For instance, in a recent report of the formation of spiro compounds by Hashmi *et al.*,[122] mononuclear NAC-gold catalysts gave exceptionally high turnover numbers even on gram scale, although the turnover numbers were reported to be dependent on the type of reaction.

4 Alkaloids

4.1 Cyclization by nitrogen or carbon nucleophiles

Lycopodium alkaloids, which are a large family of natural products with diverse biological activities and intriguing molecular skeletons, have provided suitable challenges to a variety of novel methodologies and synthetic strategies, and efforts in this areas have intensified in the last decade.[123–134] Among the members isolated to date, (+)-lycopladine A (**102**, Scheme 14) shows selective cytotoxicity towards murine lymphoma L1210 cells, and features a *cis*-fused 5,6-bicyclic ring system containing an all-carbon quaternary center that is common to all members of this family.

In terms of the total synthesis of these compounds, Toste *et al.*[135] developed a strategy that differed from those of several other groups by employing a gold-catalyzed transformation in their total synthesis of (+)-lycopladine A. The key feature of Toste's synthetic strategy involved the diastereoselective 5-*endo*-dig annulation of silyl enol ether **99** to generate the hydrindanone core **101**, where the quaternary carbon was installed through an expedient C–C bond forming reaction. More specifically, the required transformation was accomplished by the treatment of iodoacetylene **99** with 10 mol% [Ph_3PAuCl]/$AgBF_4$ in a co-solvent mixture of 10 : 1 CH_2Cl_2/MeOH at 40 °C, yielding hydrindanone vinyl iodide **101** in 95% yield as a single diastereomer. Notably, the vinyl iodide remained intact and demonstrated that this group was less prone to undergo oxidative addition in the gold-catalyzed process than other d^{10}-

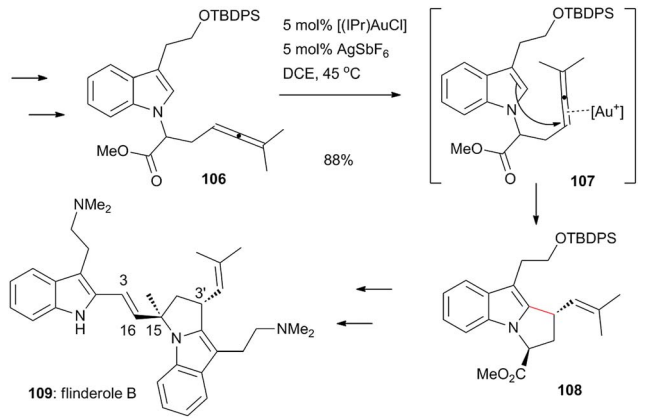


Scheme 14 Total syntheses of (+)-lycopladine A and (+)-fawcettimine.

transition-metal catalyzed reactions. Toste *et al.*[44] further extended this method in their synthesis of another *Lycopodium* alkaloid (+)-fawcettimine (**105**).[44] In this case, the gold-catalyzed cyclization of silyl enol ether **103** gave the *cis*-fused 5,6-bicyclic ketone **104** bearing a vinyl iodide ready for the attachment of other flexible functionalities. Most recently, a similar gold-catalyzed 6-*endo*-dig annulation of a silyl enol ether was employed by Li *et al.*[136] to construct a critical C–C bond in the first total synthesis of daphenylline, which is a complicated natural product from the *Daphniphyllum* alkaloid family.

In another elegant piece of work, Toste *et al.*[137] reported the convergent synthesis of the antimalarial bisindole alkaloid including flinderole B (**109**, Scheme 15), as well as its C3′ diastereomer, flinderole C, using a gold-catalyzed intramolecular hydroarylation reaction.[137]

The motivation for synthesizing flinderoles lies not only in their biological activity but also in their structural novelty. For instance, these compounds contain a C3/C16 *trans*-disubstituted olefin, as well as pyrrolidine ring attached to an isobutenyl side-chain on the eastern portion of the molecule and a quaternary methyl center at C15. In the key step highlighted in Scheme 15, allene **106**, which was prepared from commercially available tryptophol, was treated with *in situ* generated $IPrAuSbF_6$ in 1,2-DCE at 45 °C, which initiated the attack of the C2 position of the electron-rich indole on the allene, which was coordinated to the gold catalyst (*cf.* **107**). Subsequent protonolysis of the resulting C–Au bond completed the allene hydroarylation process to afford the desired pyrrolidine **108** as a single diastereomer in 88% yield. A reduction in the loading of the gold catalyst to 2 mol% was also suitable for the generation of the desired product, albeit in lower yield (81%) because of the unwanted diene side products. Overall, the gold-catalyzed intramolecular hydroarylation of the pendant allene allowed for the formation of the pyrrolidine ring and the attachment of the C3′ isobutenyl fragment, which was amenable to further derivatization.



Scheme 15 Total syntheses of flinderoles B and C.

(−)-Rhazinilam and (−)-rhazinicine (**116** and **115**, Scheme 16), are members of the Aspidosperma class of alkaloids, which consist of an unique nine-membered lactam ring skeleton fused to the tetrahydroindolizine core, as well as a quaternary carbon center. (−)-Rhazinilam (**116**) has been shown to interfere with tubulin polymerization and dynamics[138,139] and, together with its congener (−)-rhazinicine (**115**),[140] has been regarded as a lead compound for new antitumor agents.[141] Among the various syntheses reported to date, the synthesis reported by Tokuyama *et al.*[142] is of particular interest, because it used a gold-catalyzed cascade cyclization reaction of **110** for the construction of the highly substituted indolizinone skeleton. It was envisaged by Tokuyama that the intramolecular 6-*exo*-dig nucleophilic addition of the nitrogen atom to the gold-activated alkyne (*cf.* **111** and **112**) followed by cyclization of the resulting enamide towards the acetal (*cf.* **113**) would trigger a subsequent aromatization to afford indolizinone **114.**

Having established the viability of this process in model systems consisting of multisubstituted indolizinones, Tokuyama's group moved on to synthesize (−)-rhazinilam and (−)-rhazinicine using this key tandem process.

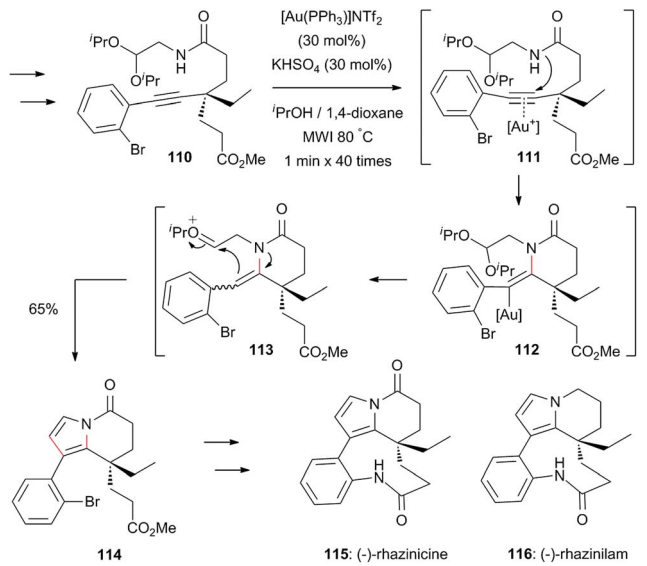
Although the steric bulk of the quaternary carbon center could have potentially slowed the initial cyclization step, which competed with several other side reactions such as the decomposition of the acetal and the gold-catalyzed methanolysis of the triple bond, the use of a sterically demanding acetal effectively suppressed the undesired conversion of the triple bond. Eventually, under optimized conditions, the desired indolizinone **114** was isolated in 65% yield. Elaboration of indolizinone **114** in five and three steps allowed for the total syntheses of (−)-rhazinilam and (−)-rhazinicine, respectively. Nelson *et al.*[143] reported a separate synthesis of (−)-rhazinilam in 2006 that also relied on a gold-catalyzed annulation, although this particular case involved the addition of a pyrrole to an allene. These syntheses are notable for their mild conditions, brevity and protection group-free chemistry.

The gold-catalyzed intramolecular alkyne hydroamination reaction provides an efficient method for the construction of versatile tetrahydroisoquinolines, as well as being complementary to the traditional synthetic methods such as Pictet–Spengler condensation.

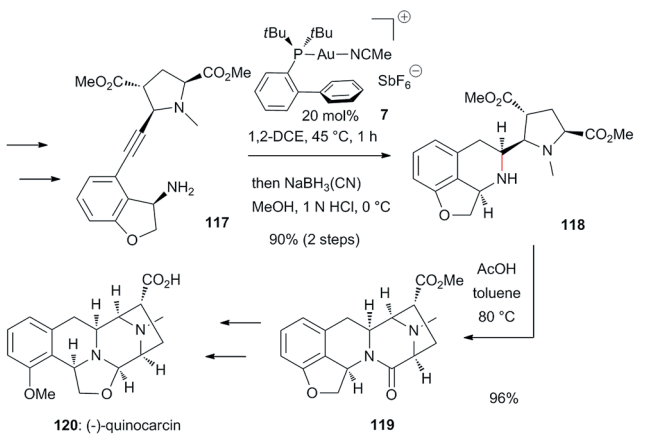
The synthesis of (−)-quinocarcin (**120**, Scheme 17) by Fuji and Ohno effectively highlights the utility of this reaction, where a gold-catalyzed regioselective hydroamination to construct the tetrahydroisoquinoline system.[144] In this particular case, the team surmised that it would be possible to generate dihydroisoquinoline *via* the 6-*endo*-dig hydroamination of an appropriate alkynyl benzylic amine substrate.

Among the transition-metal catalysts tested in a simplified model reaction, a gold catalyst was found to be the most efficient for the intramolecular hydroamination. A subsequent screen for substrates and catalysts that favored the 6-*endo*-dig cyclization over the 5-*exo*-dig cyclization led to the observation that the dihydrobenzofuran-type substrate and catalyst **7** encouraged the desired regioselective cyclization.

During the total synthesis, an *N*-Boc-protected substrate was initially prepared in a convergent manner, but attempts to affect the hydroamination of this substrate resulted in decomposition, which could be attributed to steric repulsion between the



Scheme 16 Total syntheses of (−)-rhazinilam and (−)-rhazinicine.



Scheme 17 The total synthesis of (−)-quinocarcin.

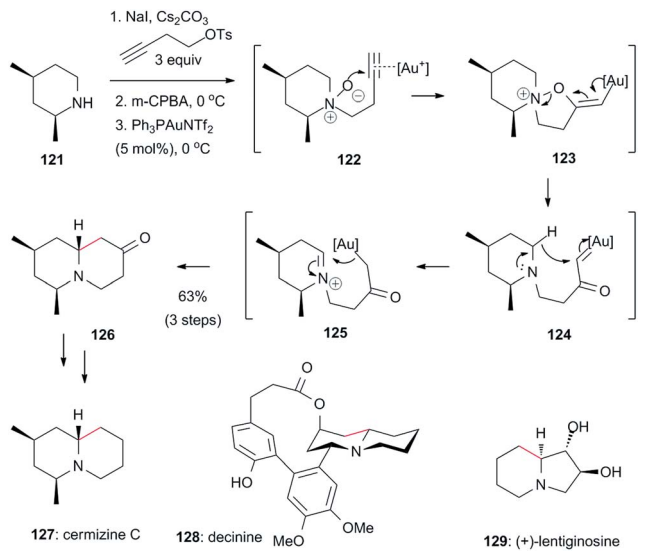
methyl ester and the Boc group. Eventually, it was found that treatment of alkynyl amine **117** with catalyst **7** (20 mol%) in 1,2-DCE at 45 °C led to the formation of the unstable dihydroisoquinoline, which in turn underwent stereoselective reduction by $NaBH_3(CN)$ to produce tetrahydroisoquinoline **118** in 90% yield over two steps. Subsequent lactamization under acidic conditions gave the diazabicyclo[3.2.1]octane core **119**, which was converted to target molecule **120** in five steps.

4.2 Gold-carbenoids leading to piperidines

Zhang *et al.*[145] reported an exceptional example of the use of a gold-catalyzed process for the construction of N-heterocycles in the context of alkaloid synthesis, where a two-step, formal [4 + 2] approach was used the diastereoselective synthesis of (±)-cermizine C (**127**, Scheme 18), which is a bioactive alkaloid consisting of a functionalized piperidine.[145]

The key feature of this approach was the expedient construction of the piperidin-4-one precursor in a regio- and diastereoselective manner. Specifically, after *N*-alkylation of 2,4-dimethylpiperidine **121** and sequential *m*-CPBA oxidation, the *in situ* generated *N*-oxide was treated with $Ph_3PAuNTf_2$ (5 mol%) in CH_2Cl_2 at 0 °C. The key step was initiated by a gold-catalyzed intramolecular oxidation of the terminal alkyne (*cf.* **122** and **123**), which afforded the α-oxo gold-carbenoid intermediate **124**. Sequential migration of the amine α-hydrogen to the gold carbene resulted in intermediate **125**, bearing both an electrophilic iminium and a nucleophilic gold enolate. Subsequent cyclization afforded piperidin-4-one **126**. The superior selectivity of the cyclization towards the less-hindered alkyl substituents, as well as the excellent diastereoselectivity of this transformation allow for broad applications. For instance, Zhang *et al.*[146] also completed the total synthesis of (+)-lentiginosine (**129**) as a more demanding target.

As part of our own work in the Yang group, we have applied identical methodology to the total synthesis of (±)-decinine (**128**) where a gold catalyzed annulation was used to form a lasubine II fragment. This novel gold-catalyzed formation of piperidin-4-one represents a formal C–H insertion and appears to compare favorably to the related Rh-catalyzed C–H insertions, which require the use of hazardous diazo starting materials. Furthermore, these reactions are invariably limited by basic amines, which can coordinate to and poison the rhodium catalyst. Using a similar strategy to that involved in the intramolecular oxidation of gold-activated alkynes through a tethered amine oxide to generate an α-oxo gold-carbenoid intermediate, Zhang *et al.*[147] also developed a cascade reaction involving a tethered azide that was followed by an electrocyclic ring closure to give a fused pyrrole ring system, and this strategy was applied to their formal synthesis of 7-methoxymitosene.



Scheme 18 The total synthesis of (±)-cermizine C, and the structures of decinine and (+)-lentiginosine.

5 Conclusions

The studies highlighted in this review capture only some of the most impressive achievements associated with the application of gold-catalyzed transformations to the synthesis of complex natural products. As our overall understanding of these reaction mechanisms improves, so too will our ability to discover and achieve new creative disconnections for target molecules using the unique reactivity of gold catalysis. For instance, in most of cases highlighted above, the gold-catalyzed reactions were terminated by proto-deauration of the resulting carbon–gold bond, with the gold catalyst being used as a hydrogen equivalent. In terms of significantly expanding the scope of reactions for organogold chemistry, one area currently experiencing rapid growth is the field of gold-catalyzed cross-couplings involving the Au^I/Au^{III} redox cycle,[25–34] and transmetalation processes involving the interception of catalytic organogold intermediates have also attracted considerable attention.[148] Another example is the predominant formation of five- and six-membered rings during gold-catalyzed cyclization reactions, which could be supplemented by gold-catalyzed methods for the construction of medium rings as well as large macrocycles.[149–153] Furthermore, enantioselective versions of various gold-catalyzed transformations will certainly become more important in terms of their practical significance.[21,154–164] Last but not the least, based on the versatility of gold-catalyzed reactions, the development of novel efficient tandem processes will continue to flourish, especially in terms of the functional group compatibility and scalability of these processes, which could be further improved. Gold catalyzed processes will undoubtedly continue to be applied to the total synthesis of natural products for many years to come, and will most likely play increasingly important roles in achieving the synthesis of even more complex and diverse target molecules.

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