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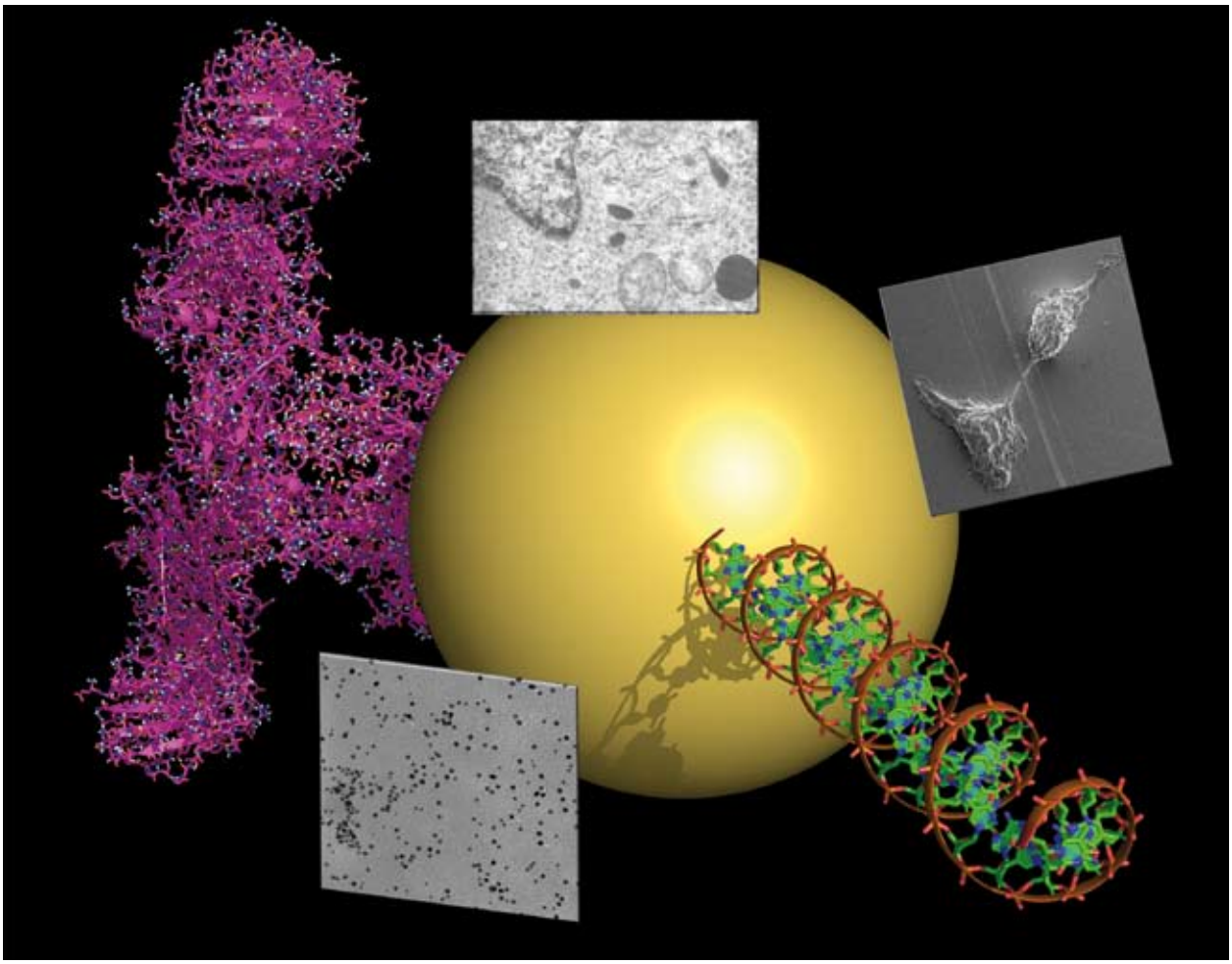

Gold catalysis in total synthesis†

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In this *tutorial review* directed towards chemists interested in synthesis or catalysis, the application of gold catalysis in total synthesis is summarised and the mode of activation of the substrate by the gold catalyst is discussed.

1. Introduction

In the past decades, the catalysis of organic reactions by transition metals has become an essential tool for both bulk and fine chemical synthesis.[1] Nature provides only 82 non-radioactive chemical elements as building blocks to chemists, but gold has only recently been investigated as a catalyst. This neglect of one chemical element in catalysis research was probably caused by two prejudices: (1) the assumption that gold is so expensive that it is unaffordable as a catalyst and (2) the inertness of gold, which with 1.48 V has the highest normal potential of all metals. But if one studies metal prices, technically important catalysis metals like rhodium and platinum are significantly more expensive than gold. Furthermore, gold is not unreactive—in the form of complexes of gold ions it has proven to catalyse many *organic reactions*; even new conversions, previously unknown in the arsenal of synthetic methods, have become possible.

In the past seven years, the field has evolved to be a true hot spot in catalysis research,[2] and after an initial focus on methodic investigation, now a number of applications in the total synthesis of natural products have been published.

Here we will use these early examples of gold-catalysed key steps in total synthesis to:

(a) show basic reaction types of gold catalysis,
(b) show how complex the retrosynthetic starting material–product relationship can be,
(c) extract basic principles of gold catalysis from these reactions,
(d) provide an outlook to future new perspectives in gold catalysis.

The most fundamental reactivity pattern in gold-catalysed organic reactions is the activation of a C–C multiple bond, in most cases an alkyne, for the attack of a nucleophile. Without the catalyst, the reaction either does not occur at all or is very slow. Only with the gold catalyst, often a cationic gold species **1**, coordinated to the alkyne in a gold–alkyne complex **2**, is the reaction rate enhanced. Most nucleophilic groups bear hydrogen atoms (as shown in Scheme 1), and then a deprotonation–reprotonation sequence sets free the gold catalyst and the reaction product **5**. But, as we shall see in the examples, there also exist other pathways from these intermediates to different products.

Characteristic for such reactions is their isohyptic nature—the oxidation state of gold does not change in the catalytic cycle.

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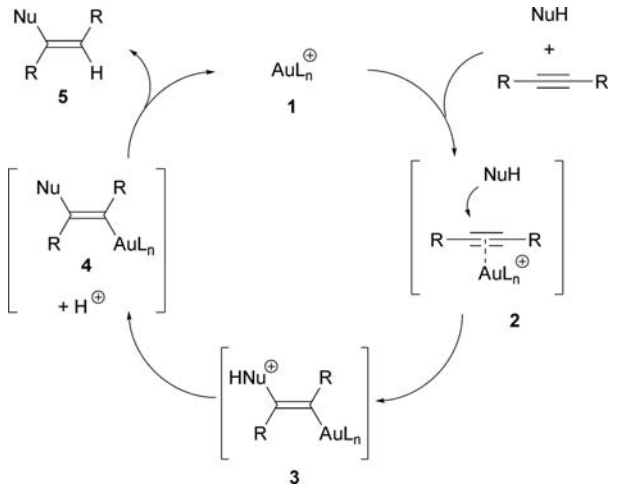


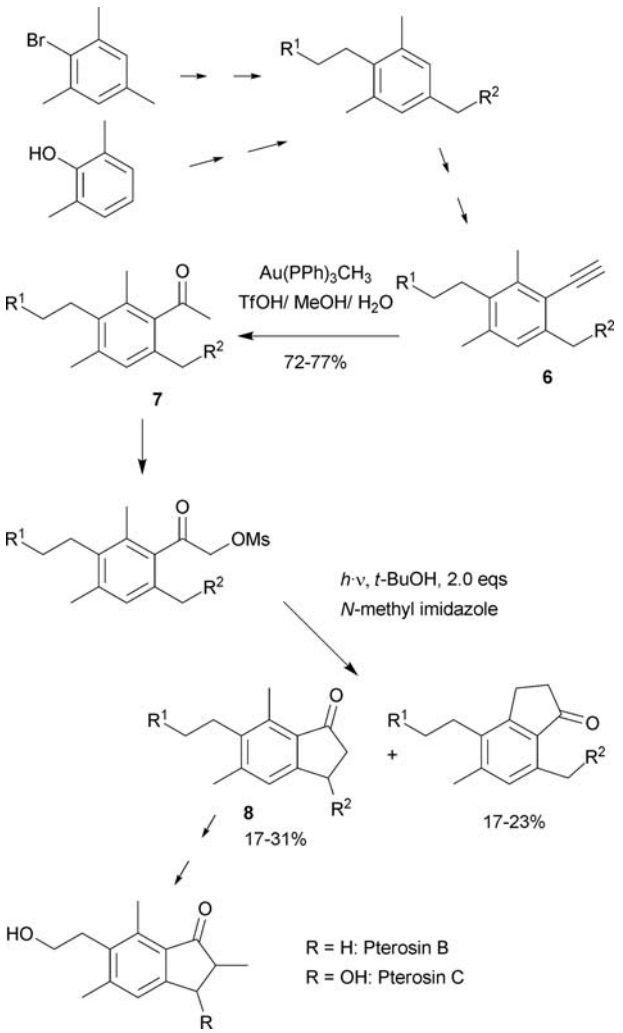
Scheme 1 The most fundamental reactivity pattern in gold catalysis.

2. Applications in total synthesis

2.1. Hydration of alkynes: Pterosins B and C

The classical method for the hydration of alkynes is the reaction with mercury(II) ions in aqueous sulfuric acid; due to the toxicity of mercury compounds this is a problematic reaction. In 1998, Teles *et al*. described the advantages of using non-toxic, kinetically highly active cationic gold(I) catalysts of type **1** for this reaction.[3]

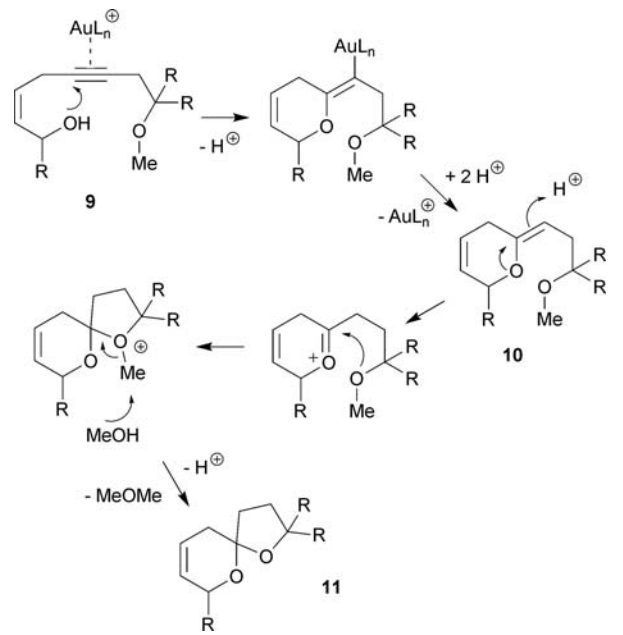
This method was used in the synthesis of Pterosin B and C (Scheme 2).[4] The selective introduction of the acyl group in **7** was achieved by the gold catalysed hydration of the ethynylarene **6**. A subsequent key step was the photochemical ring closure, a Norrish–Yang reaction with low selectivity. From the product isomer **8**, the natural products could ultimately be obtained. The selective introduction of the ethynyl group to the arene was achieved by a Sonogashira coupling. Mechanistically, the reaction follows the pathway in Scheme 1, the initially formed enol then tautomerises to the corresponding ketone. The observed Markovnikov regioselectivity of the addition step is typical for these gold catalysed reactions. Retrosynthetically, the product–substrate relationship here is an easy one, a terminal alkyne delivers a methyl ketone.



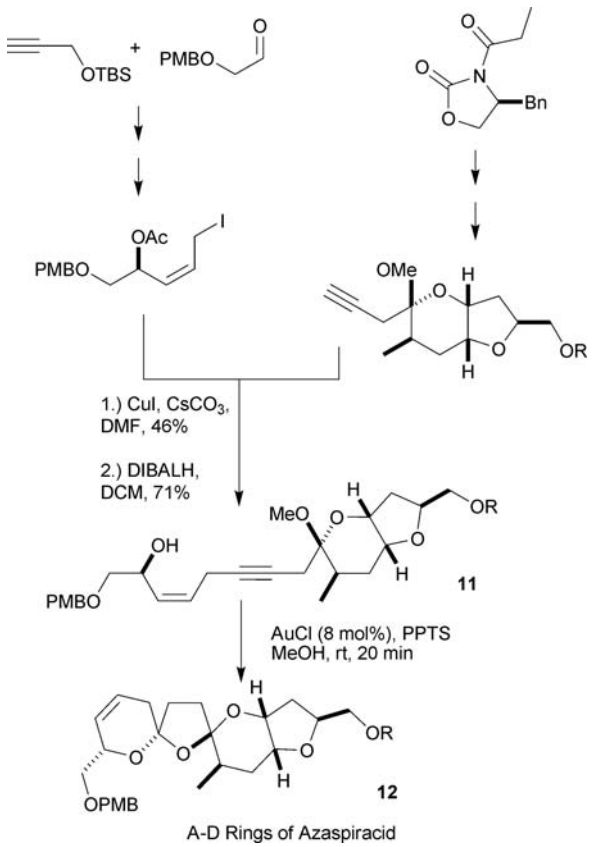
Scheme 2 Sequence leading to Pterosins.

2.2. Bis-spiroketalisation of alkynes: A–D rings of Azaspiracid

An extension of the principle described in the previous section, is the formation of spirocycles by a two-fold intramolecular nucleophilic addition (Scheme 3).[5] The (*Z*)-double bond in **9** supports the 6-*exo*-dig attack leading to product **10**. Now the electron-rich enol ether is set up for protonation and a second nucleophilic addition, this time by the methoxy group in a 5-*endo*-trig manner, which closes to a [6,5]spiroketal. Overall, the distance between the nucleophilic groups determines the regioselectivity of the addition step. In the retrosynthetic analysis, the ketalic carbon originates from an alkyne, and the geometry of the first attack at the alkyne unit must be feasible (for example as above a 6-*exo*-dig ring closure); due to the sp^2-geometry of the enol ether, the second nucleophilic attack then is much easier.



Scheme 3 Basic mechanism of the spiroketalisation.



Scheme 4 Synthesis of a section of Azaspiracid.

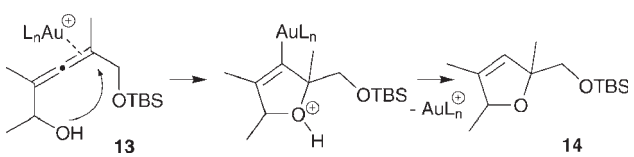
This strategy was used in the synthesis of the A–D rings of the toxin Azaspiracid (Scheme 4).[6] With the alkyne in **11** instead of a ketone as the precursor for the ketal, there was no danger of alkene isomerisation (migration into conjugation with the carbonyl group). Substrate **11** was efficiently built from simple building blocks and readily cyclised to the bis-spiroketal in **12** when subjected to AuCl under acidic conditions.

The diastereoselectivity in the ketal formation is based on thermodynamic control.

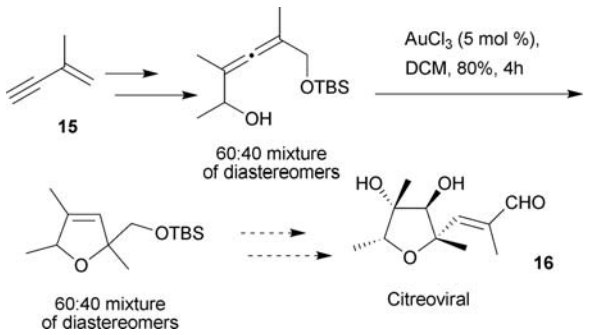
2.3. Intramolecular hydroalkoxylation of allenes: Citreoviral, (−)-isocyclocapitelline and (−)-isochrysotricine

Not only alkynes, but also allenes can be activated for the addition of oxygen nucleophiles. In the case of allenyl carbinols **13**, the dihydrofuran **14** is obtained by a 5-*endo*-trig cyclisation, the latter proceeds with an excellent axial to central chirality transfer (Scheme 5).[7]

This was used in a formal total synthesis of Citreoviral (**16**), a metabolite of the antiparasitic mycotoxin Citreoviridin (Scheme 6). Starting from 1,3-enyne **15**, the gold catalyst was crucial for the success of the cyclisation. As previously



Scheme 5 Selective cyclisation of allenyl carbinols.



Scheme 6 Citreoviral *via* an allenyl carbinol and dihydrofuran.

demonstrated by Marshall, subsequent oxidation and further modification of the side-chain delivered **16**.[7]

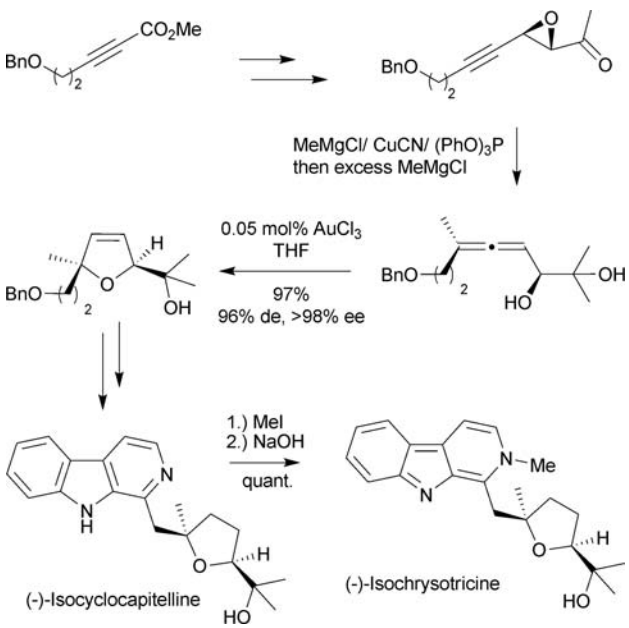
Similar allene cyclisations have been applied in the enantioselective total syntheses of (−)-isocyclocapitelline and (−)-isochrysotricine (Scheme 7).[8]

In the retrosynthetic analysis, a dihydrofuran ring is disconnected to an allenyl carbinol.

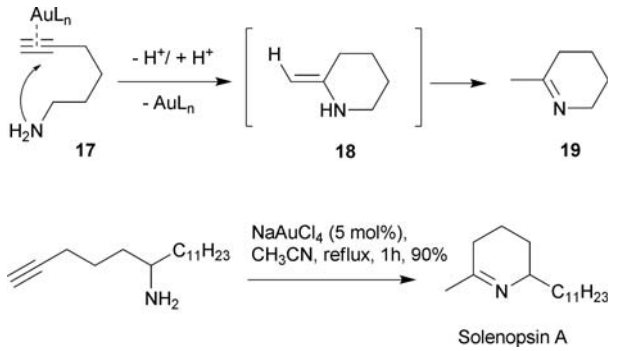
2.4. Intramolecular hydroamination of C–C triple bonds: (±)-Solenopsin A, Communesin B and Andrachcinidine

Initially, Utimoto and co-workers reported the gold(III)-catalysed hydroamination of alkynes. With alkynes like **17**, possessing a primary amine nucleophile, a 6-*exo*-dig cyclisation delivered the enamine intermediates **18** which then tautomerised to the more stable imines **19**, thus delivering tetrahydropyridines (Scheme 8). (±)-Solenopsin A and related ant venom constituents were prepared with this methodology.[9]

The gold(I) catalysed hydroamination of alkynes could be used as one step in a synthetically efficient path to the complex, hexacyclic core of Communesin B. Since a secondary amine is used as the nucleophile in the step **20** to **21**, here no subsequent isomerisation of the enamine (to an imine comparable to **19**)



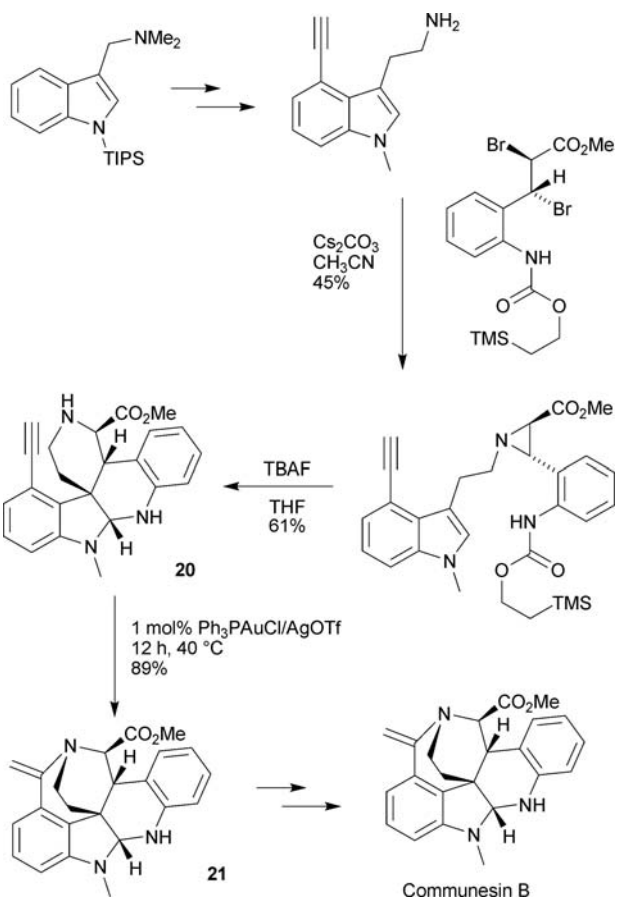
Scheme 7 (−)-Isocyclocapitelline and (−)-isochrysotricine *via* an allenyl carbinol and dihydrofuran.



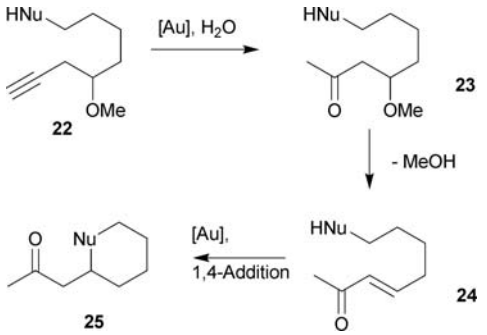
Scheme 8 Intramolecular hydroamination leading to cyclic imines like Solenopsin A.

was observed (Scheme 9).[10] The yield in this gold catalysed step of the sequence clearly exceeds the yields of the previous, more "classical" steps. In the retrosynthetic analysis, this means that an imine originates from an alkyne and a primary amine, and an enamine originates from an alkyne and a secondary amine.

An interesting combination of a gold-catalysed addition of water to a homopropargylic ether **22**, an elimination of methanol from the intermediate **23**, and a final gold-catalysed intramolecular 1,4-addition of an oxygen or nitrogen nucleophile to **24** in a 6-*exo*-trig-manner delivers either a tetrahydropyran or piperidine ring **25** (Scheme 10).



Scheme 9 Intramolecular hydroamination leading to a cyclic enamine in Communesin B.



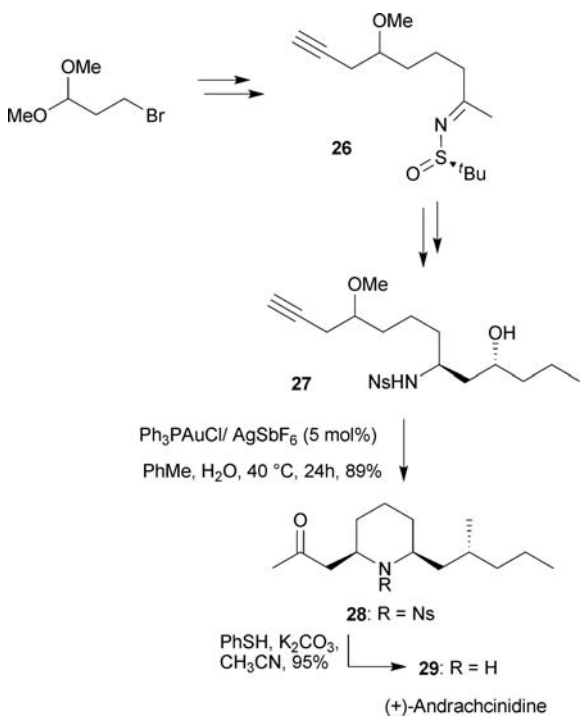
Scheme 10 Combination of two gold-catalysed steps.

This was used in the construction of Andrachcinidine (**29**, Scheme 11).[11] The enantiomerically pure sulfinylimine **26** was used to control the stereochemistry in the product, but with the resulting sulfinamide the catalysis failed and the protecting group had to be exchanged to nosyl in **27**. After the gold-catalysed cyclisation to **28** and deprotection, **29** was obtained.

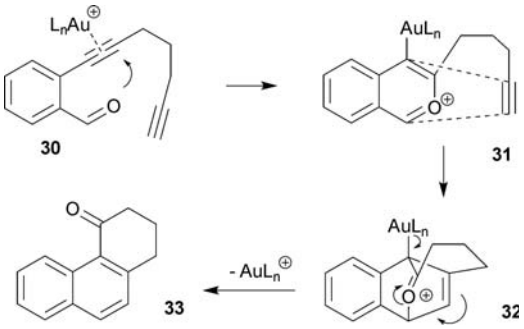
2.5. Pyrylium intermediates from *o*-alkynyl acylarenes

Another kind of nucleophile is the carbonyl group. In substrates **30**, the initial nucleophilic attack leads to pyrylium intermediates **31** which then are capable of cycloadditions to give intermediates **32**, and subsequent fragmentation leads to acylnaphthalenes **33** as the final products of this domino reaction (Scheme 12).

This transformation is not straightforward in the retrosynthetic analysis. A new arene ring is formed from two carbon atoms of a second alkyne, one carbon atom of the formyl group, the benzylic carbon atom of the benzo-conjugated alkyne and two carbon atoms of the existing benzene ring. The second carbon atom of the



Scheme 11 (+)-Andrachcinidine from a homopropargyl ether.



Scheme 12 Pyrylium intermediates as a route to annelated acylnaphthalenes.

benzo-conjugated alkyne becomes the acyl carbon connected to the 1-position of the naphthalene system.

2.5.1. (+)-Ochromycinone/(+)-Rubiginone. The auxiliary-controlled synthesis of the enantiomerically pure diyne **34** and a subsequent cross-coupling with **35** delivered the synthetic intermediate **36**. The subsequent gold-catalysed step delivers **37**, which after oxidation provides (+)-Rubiginone in excellent yield. The latter can then be demethylated to (+)-Ochromycinone (Scheme 13).[12]

2.5.2. Heliophenanthrone. A similar intramolecular cycloaddition of the pyrylium ion was the basis for the synthesis of Heliophenanthrone (Scheme 14).[13] In the cyclisation of **38** to **39**, platinum catalysts turned out to be more effective than gold catalysts, a clear proof for the necessity to conduct the corresponding control experiments.

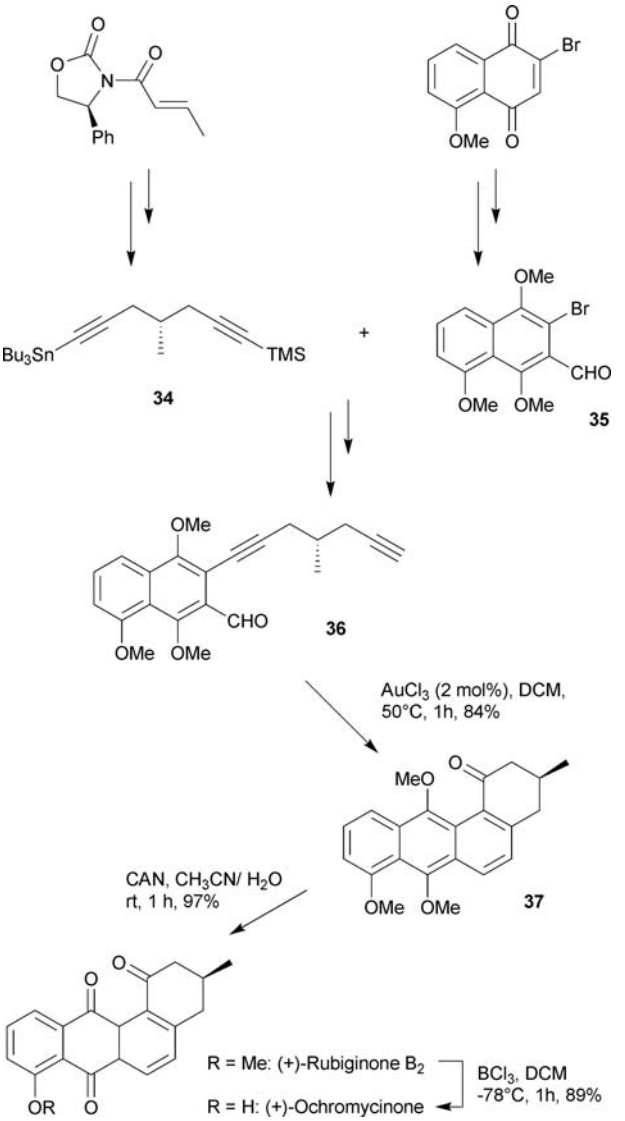
2.5.3. (±)-S-15183a. A different reactivity of the intermediate pyrylium ions was used in the synthesis of (±)-S-15183a. Rather than being converted in a cycloaddition reaction, the intermediate pyrylium ion **40** is oxidised to **41** (Scheme 15). A prerequisite is the annelation to the phenol ring which allows the efficient oxidation.[14] This synthesis allows an easy variation of the products at C3 by using other substrates in the Sonogashira coupling. The mixture of IBX and TBAI is an excellent alternative to lead tetraacetate which was used as the oxidant in a previous investigation.

2.6. Vinyl carbenoid intermediates from propargyl esters: carene terpenoids

Propargyl esters **44** are unique substrates in gold-catalysed reactions. They can be used for the cyclopropanation of olefins to deliver cyclopropanes **42** (Scheme 16).

A classical route for such cyclopropanations is the reaction of diazo compounds like **45** with alkenes in a transition-metal catalysed reaction. The retrosynthesis again is quite complex, the distal alkyne carbon of the propargyl ester together with the alkene forms the cyclopropane ring, the proximal alkyne carbon atom is oxidised to a carbonyl carbon in the product, and the former propargylic carbon atom is de-oxygenated.

2.6.1. 2-Sesquicarene. The gold-catalysed conversion of propargyl esters allowed an easy entry into terpene systems like Sesquicarene *via* the cyclopropanation of **46** to **47** (Scheme 17).[15]



Scheme 13 Synthetic application of the gold-catalysed isomerisation of *o*-alkynyl acylarenes for the synthesis of quinones.

As shown in the next section, similar strategies were applied for the synthesis of the structurally related terpenes.

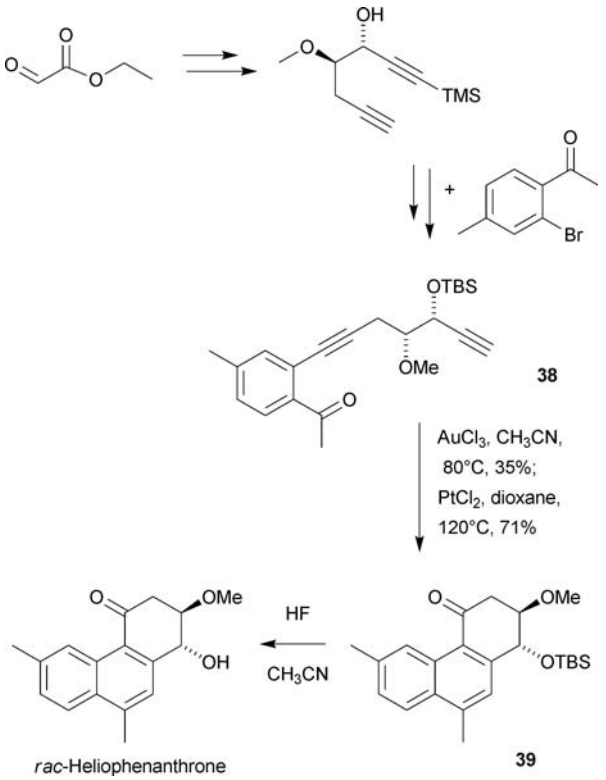
2.6.2. 2-Carene. A quite similar reaction of the easily accessible substrate **48** delivered the bicyclic core of 2-Carene in **49** in an excellent yield (Scheme 18).[15]

Related work described the synthesis of (−)-Cubebol and compares copper, platinum and gold catalysts.[16]

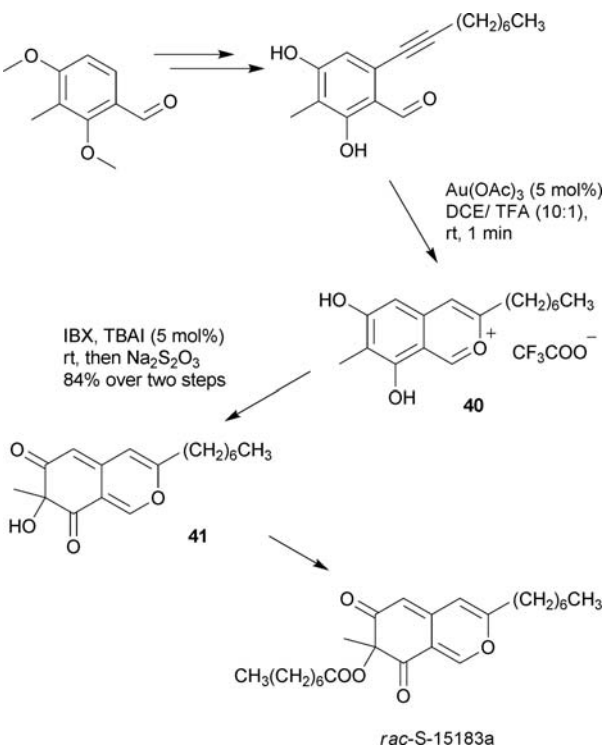
2.7. Intramolecular hydroarylation of allenes: (−)-Rhazinilam

Pyrroles are electron-rich heteroaromatic systems which easily undergo electrophilic substitution in the 2-position of the ring. Allenes of type **50** have been used as intramolecular electrophiles, here the gold catalyst allows efficient annelation of the pyrrole to a six-membered ring in the product **52**. The mechanism probably includes a vinyl–gold species **51** (Scheme 19).[17]

The application in the synthesis of Rhazinilam shows a highly diastereoselective conversion of **53** (dr = 97 : 2; Scheme 20),

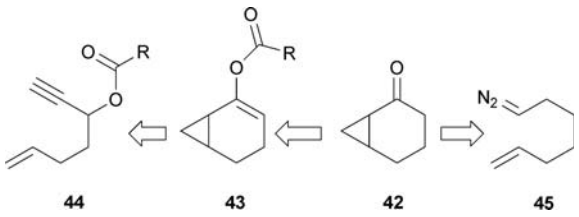


Scheme 14 Synthetic application of the gold-catalysed isomerisation of *o*-alkynyl acylarenes in the synthesis of *rac*-Heliophenanthrone.

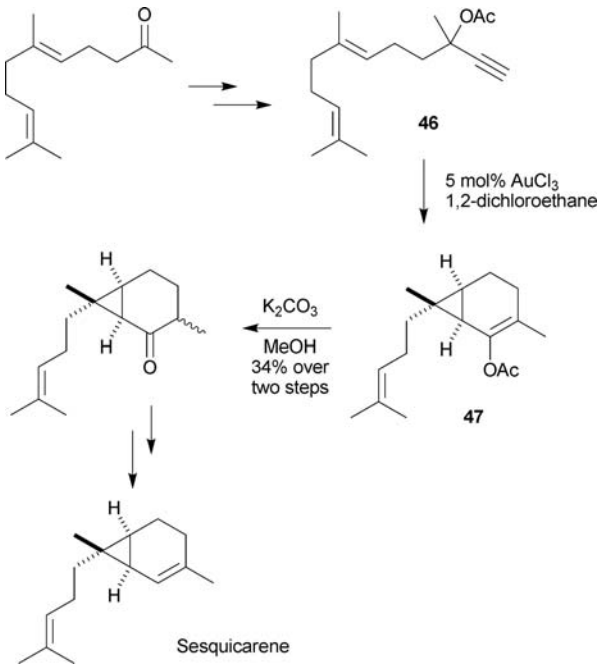


Scheme 15 Pyrylium intermediates and their oxidation.

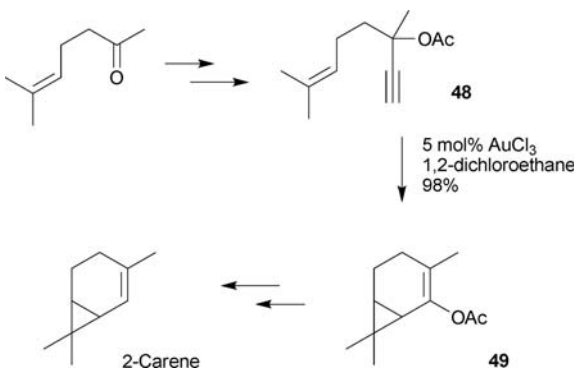
while the related palladium-catalysed conversion gave only a de of 37%. The gold(I) catalyst was superior to gold(III) chloride based catalysts.



Scheme 16 Cyclopropanation *via* propargyl esters and gold catalysts.



Scheme 17 Sesquicarene by intramolecular cyclopropanation.

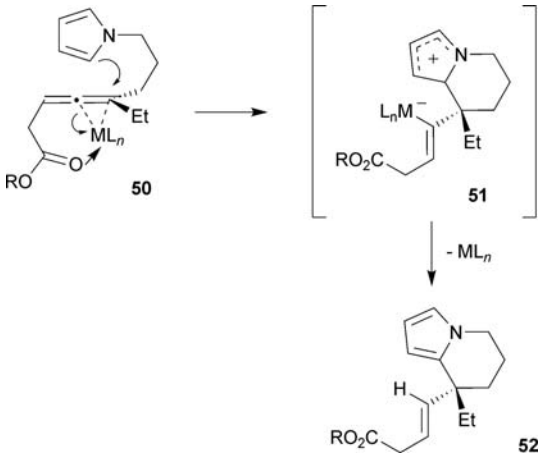


Scheme 18 2-Carene by intramolecular cyclopropanation.

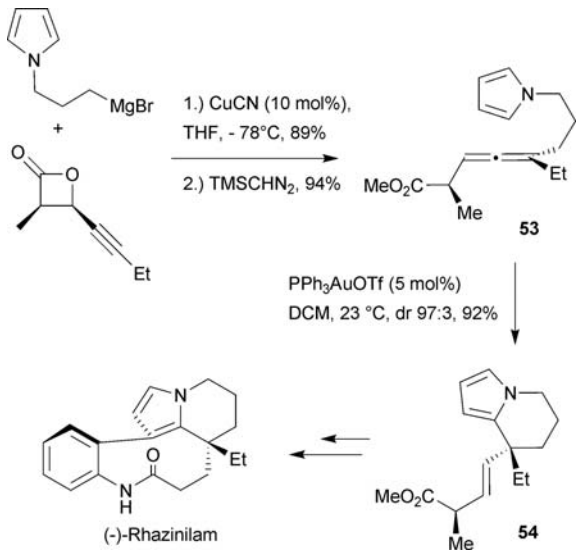
In the retrosynthetic view, an allylpyrrole originates from a pyrrole ring and an allene.

2.8. Iodoalkyne in enyne cyclisation: (+)-Lycopladine A and (+)-Fawcettimine

In the past years, gold catalysis has contributed much to the broad field of enyne cycloisomerisation chemistry.[18] Even alkynyl iodides can be converted. The silyl enol ether moiety in the 1,5-enyne **55** directly leads to the ketone in the product



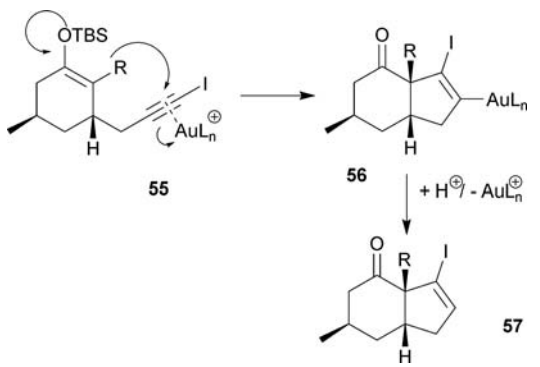
Scheme 19 Annelated pyrroles by hydroarylation of an allene.



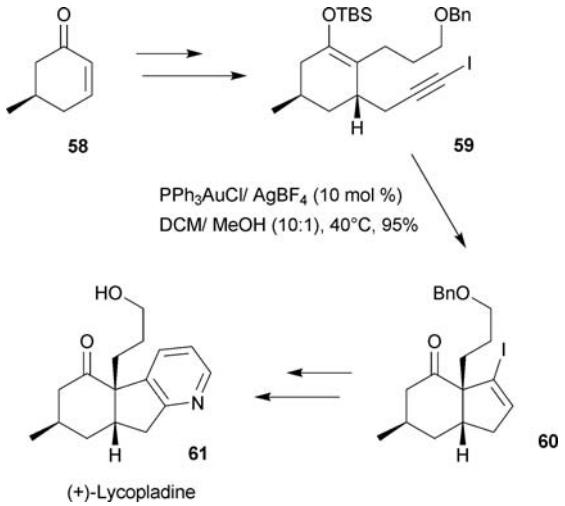
Scheme 20 Application of the hydroarylation in the synthesis of (−)-Rhazinilam.

57, again protodeauration of the vinyl–gold species sets free the product and the catalyst (Scheme 21).[19]

In the synthesis of (+)-Lycopladine A (**61**), the use of the gold catalyst provides a short route with only eight steps; the orthogonal reactivity of the gold and palladium



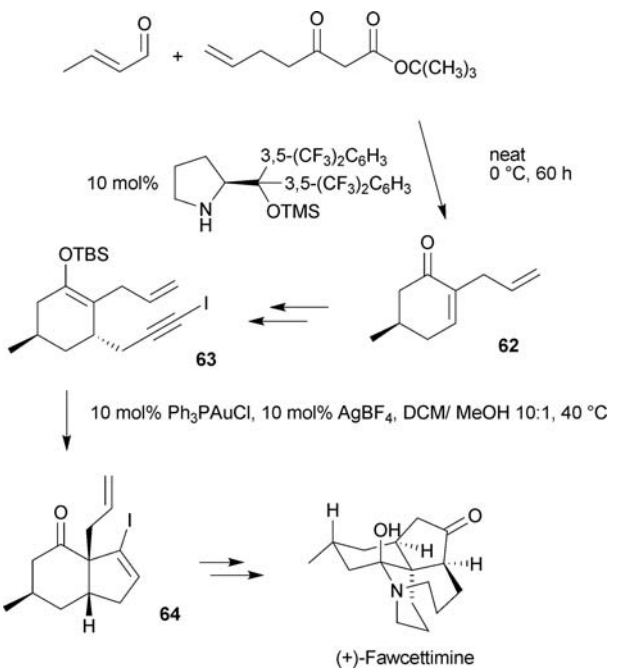
Scheme 21 A vinyl iodide by the enyne cycloisomerisation of an alkynyl iodide.



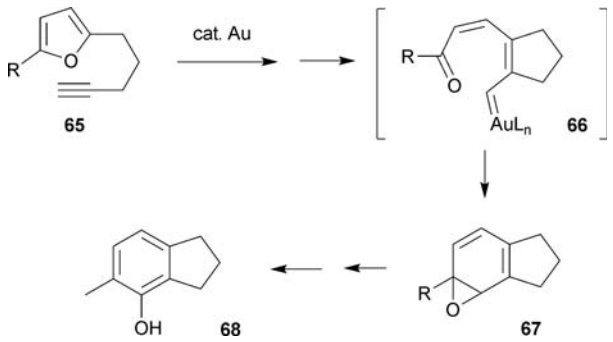
Scheme 22 Application of the enyne cycloisomerisation in the synthesis of (+)-Lycopladine A.

catalysts—gold not undergoing an oxidative addition of either the alkynyl iodide in **59** or the vinyl iodide in **60**, but palladium being able to address the vinyl iodide—is one important feature of the whole sequence (Scheme 22).

Another elegant application of this reaction principle is the synthesis of the complicated polycyclic (+)-Fawcettimine (Scheme 23). The sequence includes the formation of the first stereocentre in **62** by an elegant organocatalytic step, and the gold-catalysed formation from **63** of the hydrindanone core **64**, with the quaternary stereocentre. For the protodemetallation a proton source is necessary, since the silyl group which leaves the substrate in this step, cannot directly take care of the protodeauration.[20]



Scheme 23 Application of the enyne cyclisation in the synthesis of (+)-Fawcettimine.



Scheme 24 A new pathway in the enyne cycloisomerisation—the phenol synthesis.

A recent application of the enyne cycloisomerisation is the synthesis of a bicyclic intermediate in Nicolaou's total synthesis of Platencin.[21]

2.9. New pathway for the enyne cycloisomerisation: (±)-Jungianol

The intramolecular reaction of a furan and an alkyne (as in **65**) is another mode of the enyne cycloisomerisation. Here the product is a phenol **68**, which is formed by a complicated pathway involving gold carbenoids **66** and arene oxides **67** as intermediates (Scheme 24).

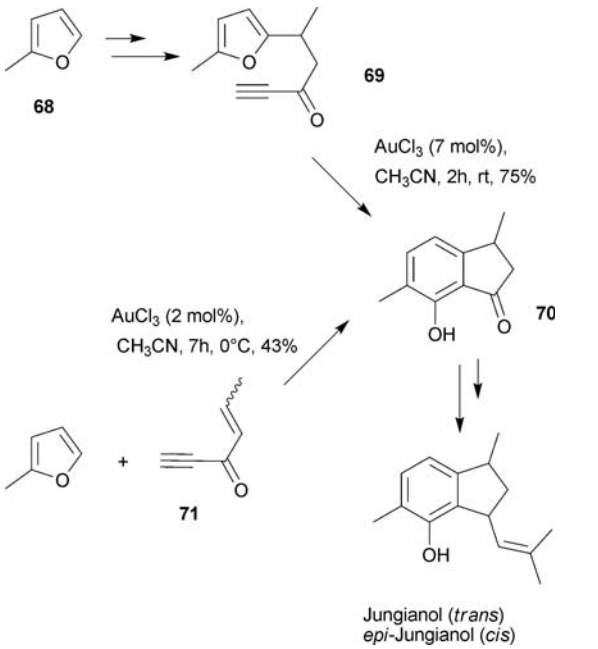
The retrosynthesis resembles a [4 + 2] cycloaddition of the furan and the alkyne and a subsequent elimination for re-aromatisation. The furan oxygen atom ultimately ends up in the phenolic hydroxyl group (at the former terminal alkyne carbon atom).

The sesquiterpene Jungianol was an ideal target for this reaction. In a sequence of six steps, beginning with simple starting materials like **68**, the two diastereomers Jungianol and *epi*-Jungianol were synthesised (Scheme 25).[22]

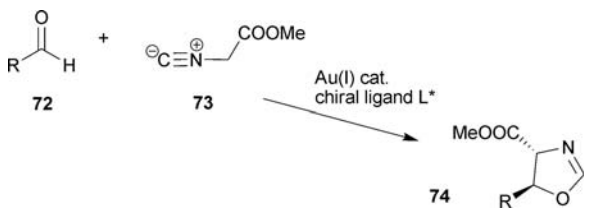
The key step was the gold-catalysed cycloisomerisation of **69** to **70**. At first glance one might suspect that an intramolecular Diels–Alder reaction and subsequent ring opening might deliver the same product **70**, but control experiments clearly proved that only the gold-catalyst opens the pathway to **70**—this finding was in accordance with the chemical databases, which did not have a single entry for the successful intramolecular Diels–Alder reaction of a substrate like **69** with a carbonyl group in the tether between the furan and the alkyne. The relative configuration of the stereocentres could be established by an X-ray crystal structure analysis of the product, which allowed a safe stereochemical assignment of the natural product for the first time. In a formal total synthesis, a gold-catalysed domino reaction consisting of hydroarylation and phenol synthesis starting from **71** even shortened the sequence.[22] In both sequences, not a single protecting group was necessary.

2.10. Catalytic asymmetric aldol reaction of isocyanoacetates and aldehydes

The asymmetric reaction of aldehydes **72** and isocyanoacetates **73** to deliver oxazolines **74** (Scheme 26) was the first gold-catalysed reaction which had significant impact on organic synthesis.



Scheme 25 Application of the phenol synthesis in the synthesis and structural assignment of Jungianol.



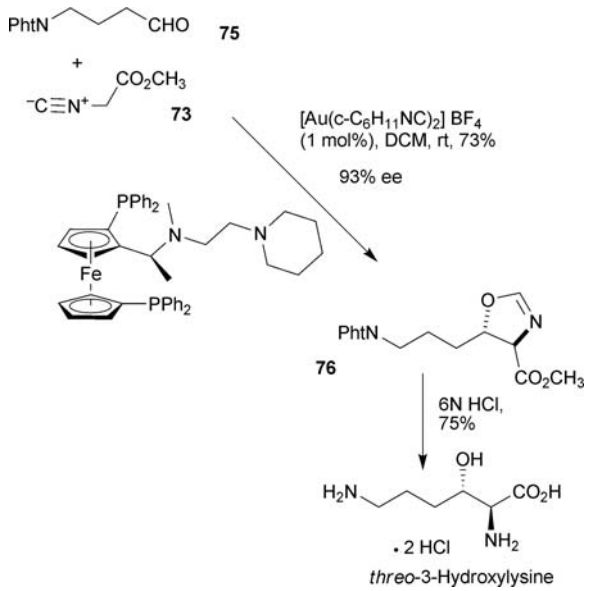
Scheme 26 The Ito–Sawamura–Hayashi asymmetric aldol reaction.

While today many chiral catalysts for aldol addition reactions are known, the gold complexes of chiral ferrocenylphosphanes in 1986 provided the first examples for catalytic asymmetric aldol reactions in the history of chemistry.[23] Most of today's cationic gold(I) catalysts are still based on this initial pioneering work.

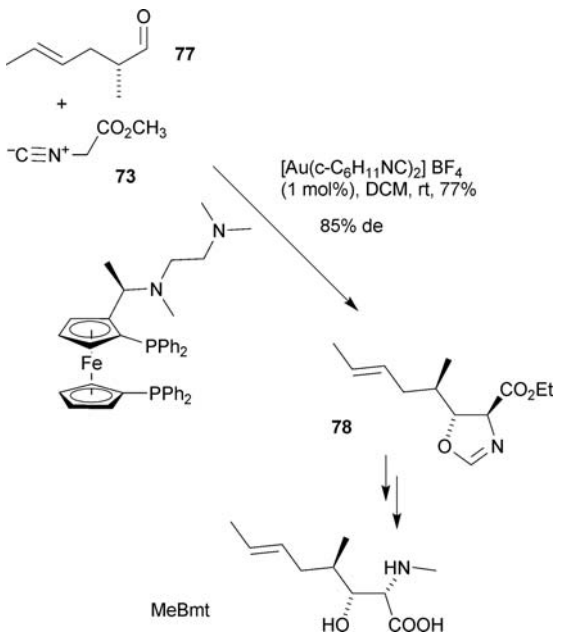
In most of the examples, the oxazoline ring is cleaved in subsequent steps, thus the motif of an α-amino-β-hydroxy carboxylic acid can be disconnected to an aldehyde and an isocyanoacetate.

2.10.1. *threo*-3-Hydroxylysine. The synthesis of the amino acid *threo*-3-hydroxylysine is one of the examples of a successful application of this reaction. Starting from the substrates **73** and **75**, the oxazoline **76** was obtained in good yield and with good enantiomeric excess (Scheme 27). Simple hydrolysis of the oxazoline ring then set free the α-amino-β-hydroxy carboxylic acid hydroxylysine.[24]

2.10.2. MeBmt. This synthesis uses the chiral aldehyde **77** as a starting material (Scheme 28).[25] The proper combination of the planar chirality at the ferrocene and the central chirality in the side chain is essential for the formation of the desired oxazoline **78** in high diastereoselectivity. The configuration of the newly formed stereocentres is controlled by the catalyst and not by the chiral substrate. From there, a few more steps deliver the unusual amino



Scheme 27 Asymmetric synthesis of hydroxylysine.

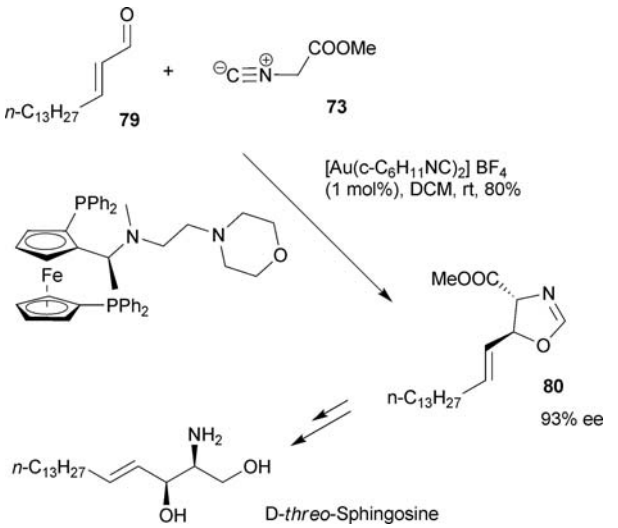


Scheme 28 Asymmetric synthesis of MeBmt.

acid MeBmt, which is part of the undecapeptide cyclosporine. This was the shortest synthesis of this compound, a clear proof of the efficiency of the sequence involving gold catalysis.

2.10.3. *threo*- and *erythro*-Sphingosines. In the synthesis of Sphingosines, the gold-catalysed oxazoline synthesis was a useful tool, too. Even the α,β-unsaturated aldehyde **79** could be converted to **80** with 93% enantiomeric excess (Scheme 29). Cleavage of the oxazoline ring and reduction of the ester group delivered the *threo*-Sphingosines. A subsequent protection and inversion of configuration at C3 by a Mitsunobu reaction made the *erythro*-Sphingosines accessible.[26]

2.10.4. (−)-α-Kainic acid. Another application of this methodology that demonstrates that even thioethers are tolerated in



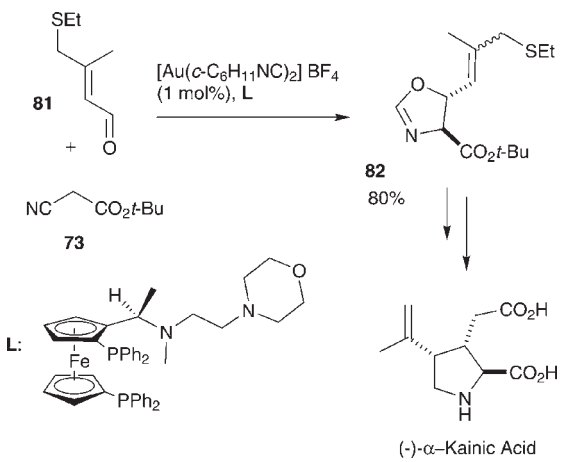
Scheme 29 Asymmetric aldol reaction in the synthesis of D-*threo*-Sphingosine.

the gold-catalysed step, is the step from **81** to **82** in the synthesis of (−)-α-Kainic acid (Scheme 30).[27] The authors only report the yield, the exact enantiomeric excess of **82** is not mentioned, but, based on the fact that after some further conversions the product was still detected as enantiomerically pure, there is good evidence for high enantiomeric purity.

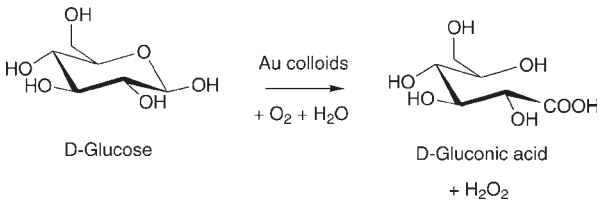
2.11. Oxidation with O_2: D-gluconic acid

Gold catalysts are capable of selectively oxidising the aldehyde group of D-glucose (drawn as the cyclic semi-acetal in Scheme 31). In this case colloidal gold is used and molecular oxygen is the oxidant. It can be shown that initially H_2O_2 is formed in the reaction, but that is decomposed *in situ*.[28] Thus this investigation indicates that, even in these oxidation reactions, gold does not change oxidation state and probably still follows the concept of an isohyptic reaction as discussed in the introduction.

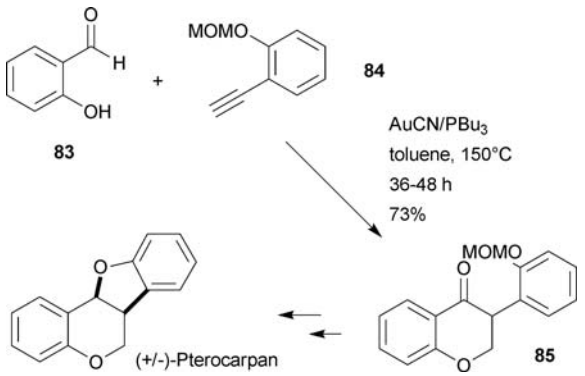
This aldehyde to carboxylate conversion is of significant economic importance.



Scheme 30 The asymmetric aldol reaction in the synthesis of (−)-α-Kainic acid tolerates a thioether group.



Scheme 31 Selective oxidation of D-glucose with molecular oxygen.



Scheme 32 (±)-Pterocarpans *via* a gold-catalysed domino alkyne addition–annelation.

2.12. Domino reactions: (±)-Pterocarpans

The addition of *o*-hydroxy benzaldehydes to alkynes, an annelation process based on a gold-catalysed domino reaction, is catalysed by gold complexes.[29] This opens an efficient route to (±)-Pterocarpan from simple building blocks like salicylaldehyde **83** and protected α-alkynylphenol **84**, which deliver a good yield of **85** (Scheme 32).

3. Conclusions

The examples above show that the early successes of methodology investigations into gold catalysis are now having an increasing impact on total synthesis. The reactions show a high functional group tolerance, for example even alkynyl iodides or vinyl iodides as well as thioethers are tolerated. Apart from diastereoselective reactions with chiral substrates, enantioselective reactions will also have a strong impact on synthesis in the future. The high synthetic efficiency of domino reactions, which combine the powerful single reaction pathways of gold catalysis, will also gain in importance.

Overall, we will probably see a similar exponential growth in the synthetic applications as we have seen in methodology investigations since the year 2000.

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