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Recent Developments in Transition Metal-Catalysed Spiroketalisation

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Abstract

The spiroketal motif occurs in a wide range of biologically active natural products and represents a valuable target in medicinal chemistry and total synthesis. In recent years, innovative new synthetic methods have substantially expanded the range of potential precursors, cyclisation modes and opportunities for asymmetric catalysis and tandem processes. This Perspective aims to highlight recent rapid advances in the use of transition metal catalysis for spiroketal formation, in the context of our own investigations into gold-catalysed asymmetric spiroketalisation.

1. Introduction

The spiroketal moiety continues to receive significant attention from the synthetic community. Spiroketals occur in numerous natural products exhibiting a wide range of biological activities and they can be considered privileged scaffolds. Recently published examples include the human telomerase inhibitor γ-rubromycin (**1**)[1], the antimitotic agent spirastrellolide B (**2**)[2], and the shellfish toxin pectenotoxin 2 (**3**)[3] (Figure 1).

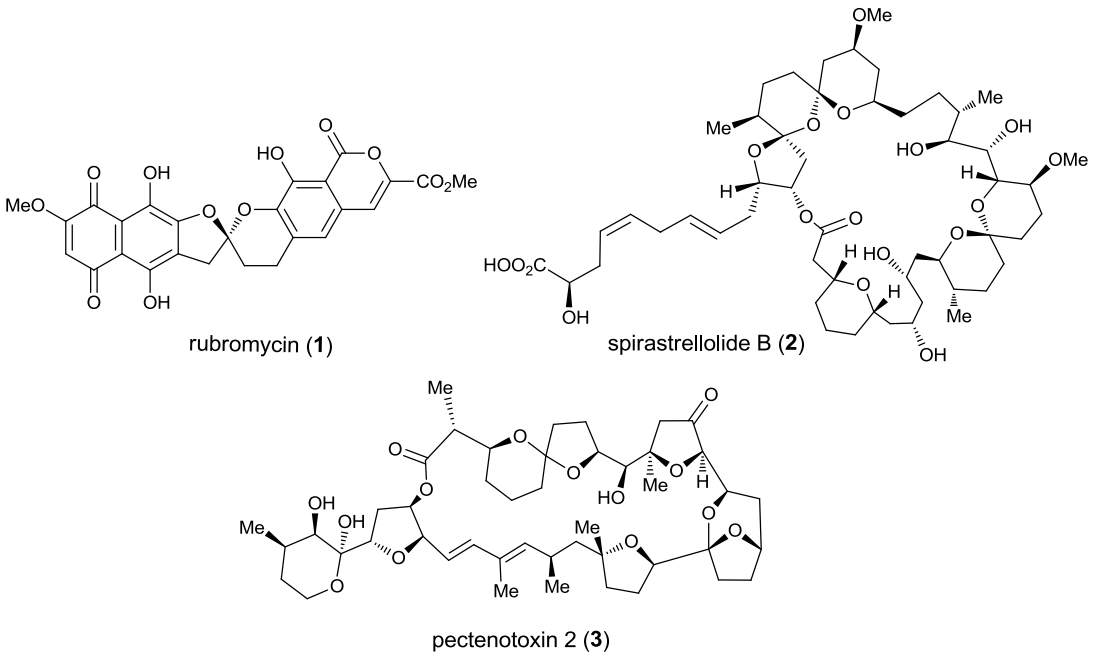
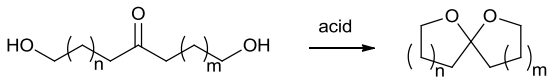


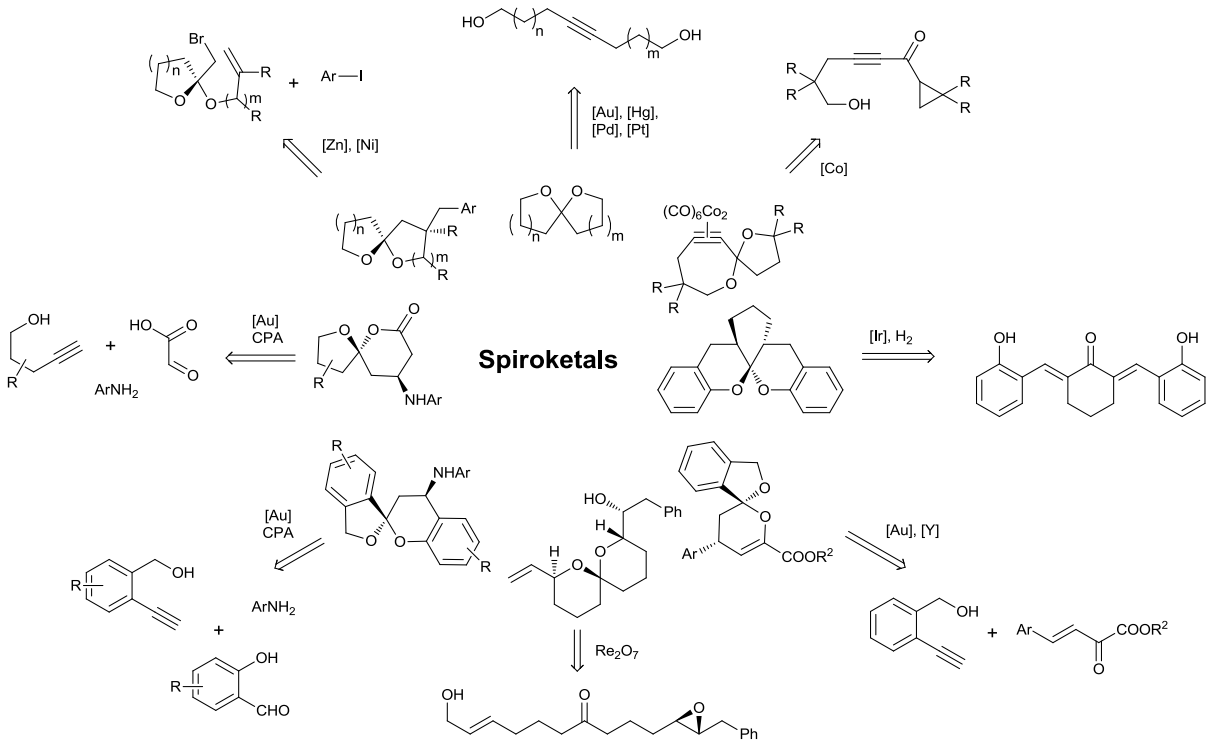
Figure 1. Selected examples of spiroketal-containing natural products

Spiroketals are commonly prepared by acid-catalysed cyclisation of dihydroxy ketones (Scheme 1). In recent years, however, a variety of new and innovative strategies for the preparation of spiroketal-containing compounds have been developed. These include transition metal-catalysed spiroketalisation of alkynes and alkenes, hetero-Diels-Alder reactions, and oxidative radical cyclisations.[4,5]



Scheme 1. Classical preparation of spiroketals

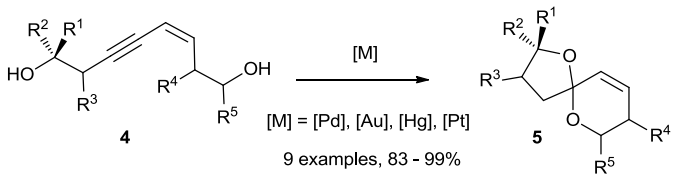
The utilisation of transition metals for the synthesis of spiroketals has attracted significant attention. In particular, Pd^{II}, Pt^{II}, Au^{I} and Re^{VII} have all been investigated for their ability to construct the spiroketal moiety. Recent developments have explored numerous novel cyclisations and their application to the synthesis of spiroketal-containing natural products. Developments include new catalytic protocols, exploration of chiral ligands and the novel application of known reactions to the synthesis of spiroketals. This Perspective covers recent metal-catalysed syntheses of spiroketals (published since 2012) in this rapidly-developing field (Scheme 2).



Scheme 2. Transition metal catalysed spiroketalisation from a range of precursors

2. Novel Substrates and Catalysts Used in Transition-Metal Catalysed Spiroketalisation

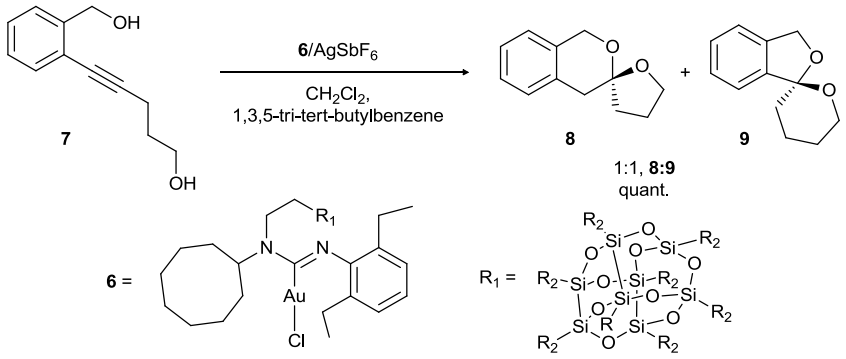
The substrate scope and functional group compatibility of transition metal-catalysed spiroketalisation continues to expand. In a recent publication by Zhdanko and Maier[6] 1,3-enyne diols **4** were efficiently cyclised in the presence of a myriad of different transition metals to produce unsaturated 5,6-spiroketals **5** (Scheme 3). The mild and selective conditions used to effect spirocyclisation are tolerated by a wide array of functional groups including non-participating unprotected alcohols.



Scheme 3. Spirocyclisation of enyne diols

One of the potential issues with transition metal-catalysed spirocyclisation onto alkynes is the possibility of different regiochemical outcomes arising from nucleophilic attack on either side of the triple bond. In the case of the 5,6-spiroketals above, regioselectivity is controlled by the kinetically favoured 5-exo-dig attack of the hydroxyl group on the side of the alkyne beta to the olefin. Interestingly, initial attempts to form 6,6-spiroketals from enyne diols with longer aliphatic chains were unsuccessful. This marked difference is attributed to competitive side reactions and decomposition which are thought to occur faster than the final cyclisation step. Despite this drawback, the wide range of catalysts and short reaction times for the production of unsaturated 5,6-spiroketals make this methodology a useful development.

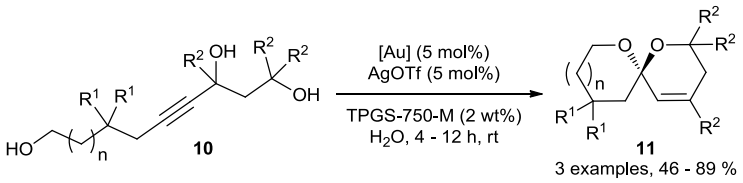
The development of novel catalytic spiroketalisation protocols has inspired the design of new ligand systems. Potent *N*-acyclic carbene (NAC) Au(I) complexes such as **6** (Scheme **4**), recently investigated by Hashmi,[7] have shown unprecedented catalytic ability both in terms of turn over number (TON) and turn over frequency (NOF). Quantitative spiroketalisation of alkyne diol **7** (Scheme 4) was achieved with extremely low catalyst loadings, providing 100% conversion at 0.00001 mol% using NHC-Au(I) catalyst **6**.



Scheme 4. NAC-Au(I)/Ag spiroketalisation catalysts

Removal of the large silicon-based cage from the ligand still enables the complex to achieve conversions of 97% at 0.0001 mol%. In probing the kinetics of these two catalysts it was found that the initial rate of conversion was the same for both catalytic systems. It is thought that the difference in conversion is due to a disparity in catalyst stability. The bulky silicon-based cage is thought to provide stability to the active complex, enabling higher TON and subsequently lower catalyst loadings.

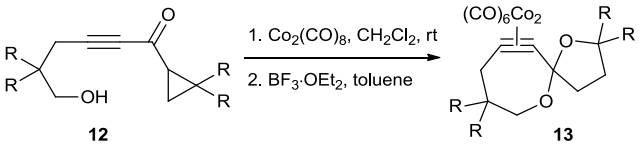
Krause and Lipshutz[8] investigated gold-catalysed spiroketalisations in water, exploiting the micellar effect to perform a tandem spiroketalisation/dehydration of trihydroxyalkyne **10** to afford a collection of unsaturated 6,6-spiroketals **11** (Scheme 5).



Scheme 5. Spiroketalisation/dehydration in surfactant containing aqueous media

The addition of catalytic quantities of a surfactant, TPGS-750-M, formed nano-micelles in which reactants are concentrated in levels higher than in an organic medium, allowing otherwise sluggish reactions to proceed quickly in high yields. The reaction was successfully catalysed by both Au(I) and Au(III) species with the best yields being observed using $AuBr_3$. The addition of Ag(I) salts did not improve conversion. When these reactions were performed in the absence of the surfactant no product was observed.

Mukai *et al.*[9] has reported the selective preparation of 5,7-spiroketals **13** using the $Co_2(CO)_6$-alkyne complex of α-cyclopropyl ketone **12** via a Nicholas reaction (Scheme 6). Such an approach represents a valuable contribution to the literature as it can often be challenging to selectively construct a 5,7-ring spiroketal system employing other spiroketalisation strategies due to the often more favourable formation of 5- and 6-membered rings in spirocyclisation.

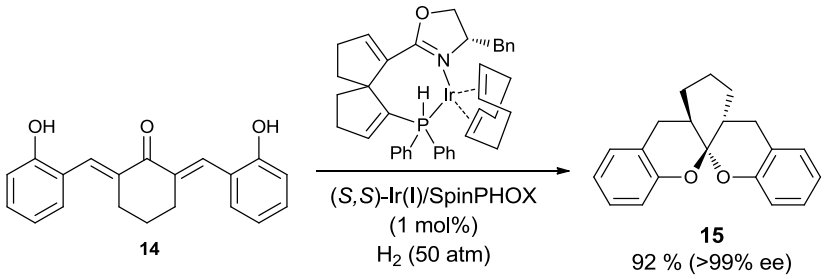


Scheme 6. 5,7-Selective spiroketalisation via a Nicholas reaction

3. Enantioselective spiroketalisations

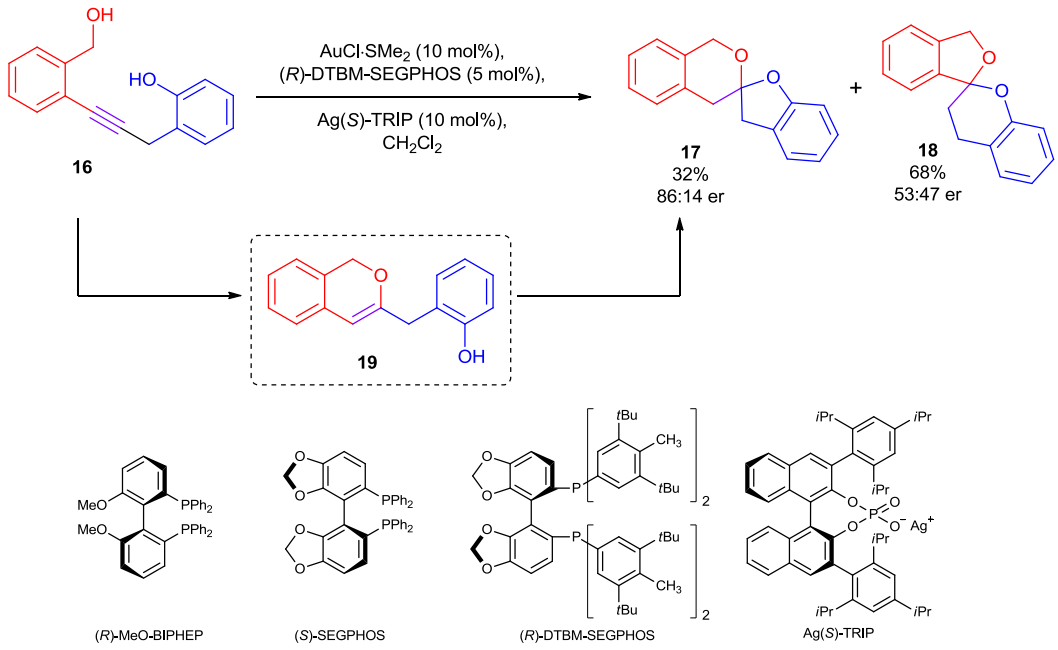
There have been significant developments in stereoselective spiroketalisation, utilising a wide array of chiral sources. This has been well illustrated in the recent publications by the work of several groups, including our own.

In 2012, Wang[10] *et al.* developed an Ir(I)/SpinPHOX-catalysed asymmetric hydrogenation/spirocyclisation of α,α'-bis(2-hydroxyarylidene) ketone **14** for the stereospecific formation of 6,6-benzannulated spiroketal **15** containing a saturated carbon bridge (Scheme 7). Interestingly, attempts at forming the spiroketal without the bridge resulted in racemic mixtures.



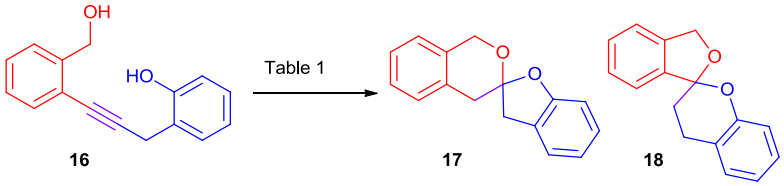
Scheme 7. Asymmetric hydrogenation/spirocyclisation

Our own recent exploration[11] of the use of chiral gold-phosphine complexes and chiral anions for the synthesis of benzannulated spiroketals has shown promising results for asymmetric spiroketalisation (Scheme 8, Table 1). The cyclisation of dihydroxyalkyne **16** yielded a regioisomeric mixture of spiroketals **17** and **18**. Spiroketal **17** was identified as the kinetic product due to an increase in selectivity for **17** when the reaction temperature was lowered from rt to -40 °C (entry 1 and 2, Table 1). Surprisingly, only spiroketal **17** was obtained with good enantioselectivity (up to 87:13 er) via the enol ether intermediate **19**.



Scheme 8. Synthesis of benzannulated spiroketals using chiral gold-phosphine complexes

Table 1. Asymmetric gold-catalysed spirocyclisation

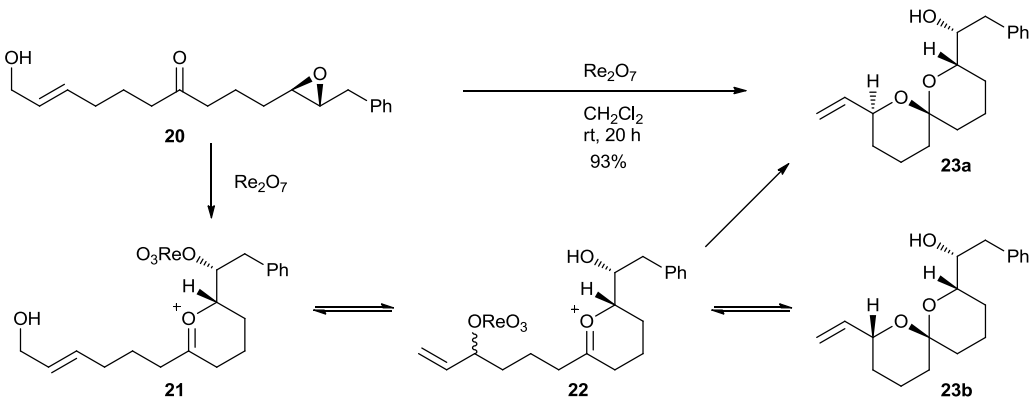


16 17 18

entry	catalyst[a]	L[b]	AgX[c]	yield[d]	**17**:**18**[e]	er (**17**)[f]	er (**18**)[f]
1	$AuPPh_3Cl$	(*R*)-MeO-BIPHEP	$AgSbF_6$	76	83:17	0	0
2[g]	$AuPPh_3Cl$	(*R*)-MeO-BIPHEP	$AgSbF_6$	96	94:6	0	0
3	-	-	Ag(*S*)-TRIP	29	68:32	53:47	84:16
4	$AuPPh_3Cl$	-	Ag(*S*)-TRIP	81	88:12	54:46	82:18
5	$AuCl{\cdot}SMe_2$	(*S*)-SEGPHOS	Ag(*S*)-TRIP	99	93:7	53:47	87:13
6	$AuCl{\cdot}SMe_2$	(*R*)- DTBM-SEGPHOS	Ag(*S*)-TRIP	99	68:32	53:47	86:14

All reactions carried out in CH_2Cl_2 at rt. [a]10 mol % catalyst. [b] Catalyst to L (2:1). [c][M] to AgX (1:1. [d]Isolated yield (%) of regioisomeric mixture. [e]Determined by ^{1}H NMR. [f]er determined by chiral HPLC. [g]Reaction at -40 °C.

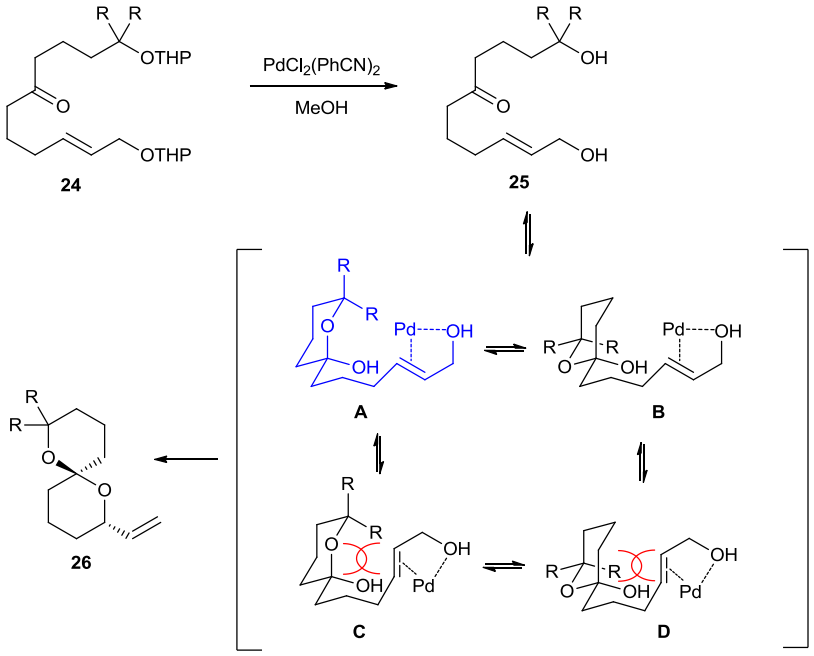
Floreancig *et al.*[12] used rhenium oxide to mediate allylic alcohol transposition using a ketone as a stereochemical conduit (Scheme 9). The chiral oxocarbenium ion **21** generated from opening the epoxide by the ketone, acts as the trapping agent for the transposed alcohol **22**, forming the thermodynamically favoured spiroketal **23a**.



Scheme 9. Rhenium oxide-mediated allylic alcohol transposition reactions

In the palladium-catalysed heterocyclisation of dihydroxyketones to synthesise 6,6-spiroketals reported by Hirai *et al.*,[13] attack of the carbonyl group by the alcohol generates a hemiketal intermediate which in turn undergoes S_N2' type substitution with the Pd-activated alcohol to afford the spiroketal **26** (Scheme 10). The stereoselectivity of the reaction results from the conformation of the hemiketal intermediate **A**. Dihydroxyketone **25** exists in equilibrium with hemiketals **A**-**D**. Hemiketal **A** and **B** are epimeric at the spiroketal centre, with **A** being favoured over **B** due the

presence of a stabilizing exo-anomeric effect between the lone pair on the hydroxy group and the σ* orbital of the C-O bond from the ring. Isomers **C** and **D** are conformational isomers of **A** and **B** respectively, involving rotation of the C-C bond adjacent to the alkene. Isomer **C** is less favoured than its conformational isomer, **A**, due to a steric interaction between the carbon chain and the six membered ring. This combination of anomeric and steric effects leads to **A** being the most favoured isomer, resulting in formation of spiroketal **26** with very high diastereoselectivity.

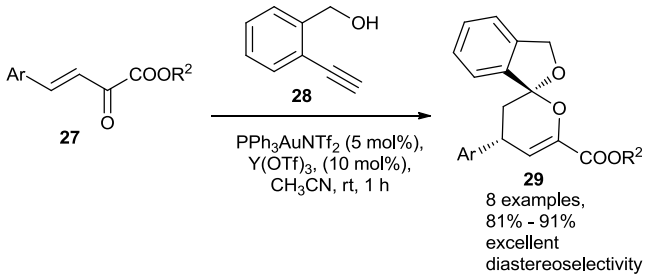


Scheme 10. Pd-Catalysed cyclisation of dihydroxyketones

4. Stereoselective Multicomponent Spiroketalisation Cascades

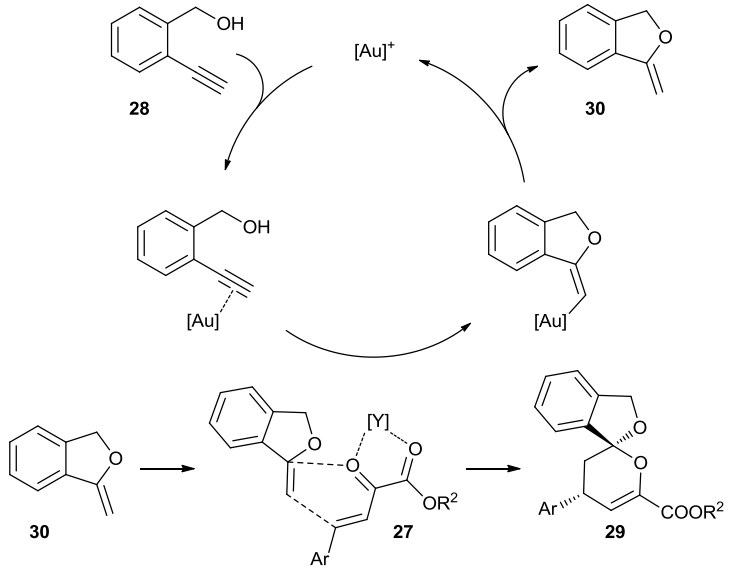
Transition metals are suitable catalysts for many organic transformations hence their ability to participate in cascade reactions is of great synthetic utility. Many examples have recently emerged in the literature which utilise transition metals to efficiently couple and cyclise fragments in one pot to form the central spiroketal moiety. This method enables access to complex substrates in a highly convergent and stereoselective manner.

Wang and co-workers[14] have utilised 'bimetallic relay catalysis' to synthesise a series of spiroketals and spiroaminals. A series of unsaturated keto-esters **27** were coupled and cyclised with alkynol **28** in the preparation of 5,6-spiroketals **29** (Scheme 11). The reactions proceeded with excellent diastereoselectivity with only the *endo* isomer detected.



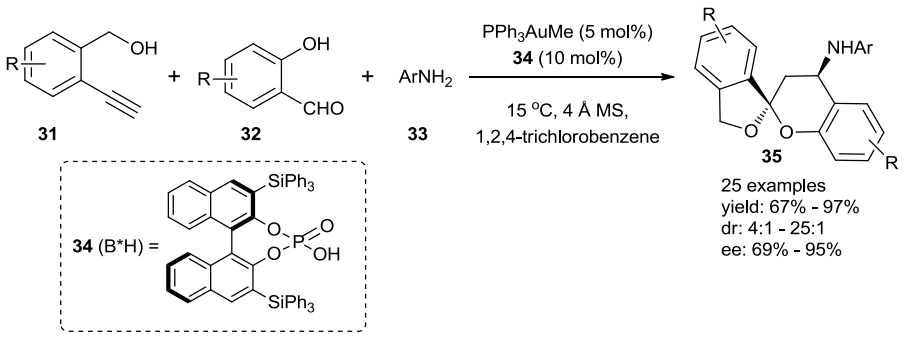
Scheme 11. Au(I)/Y(III) Bimetallic relay catalysis

Exploration of the reaction mechanism (Scheme 12) suggested that the initial step is gold-catalysed cyclisation of alkynol **28** *via* kinetically favoured 5-*exo* attack onto the triple bond. This generates nucleophile **30** *in situ* which then reacts with the electrophilic α,β-unsaturated keto-ester **27** to provide the final spiroketal product **29**. A Diels-Alder-like transition state is proposed to account for the final position of the double bond and the high diastereoselectivity observed.



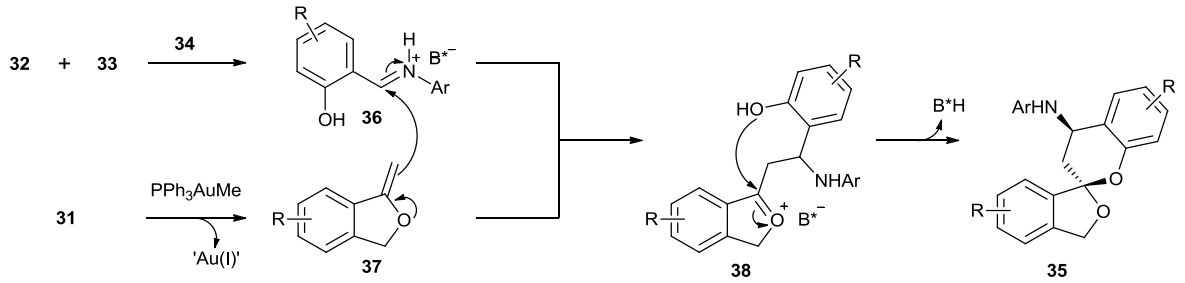
Scheme 12. Proposed reaction mechanism for Au(I)/Y(III) bi-metallic relay catalysis

Gong and co-workers[15] have also employed an *in situ* generated nucleophilic enol ether species, to couple benzannulated alkynols **31** with a series of phenolic aldehydes **32** and aromatic amines **33**. A wide variety of 5,6-spiroketals **35** were obtained in high yields with good stereoselectivity (Scheme 13).



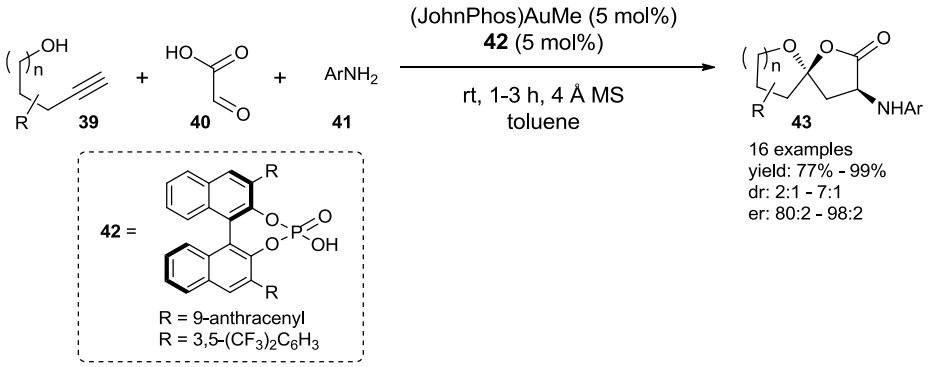
Scheme 13. Three component coupling/spiroketalisation cascade

In these reactions, generation of an iminium ion **36** is catalysed by chiral Brønsted acid **34** followed by attack from enol ether **37**, generated by gold-catalysed cyclisation of alkynol **31** (Scheme 14). The intermediate oxonium **38** may associate with the conjugate base of the chiral phosphoric acid **34** resulting in stereoselective spiroketalisation onto the oxonium ion by the phenolic oxygen.



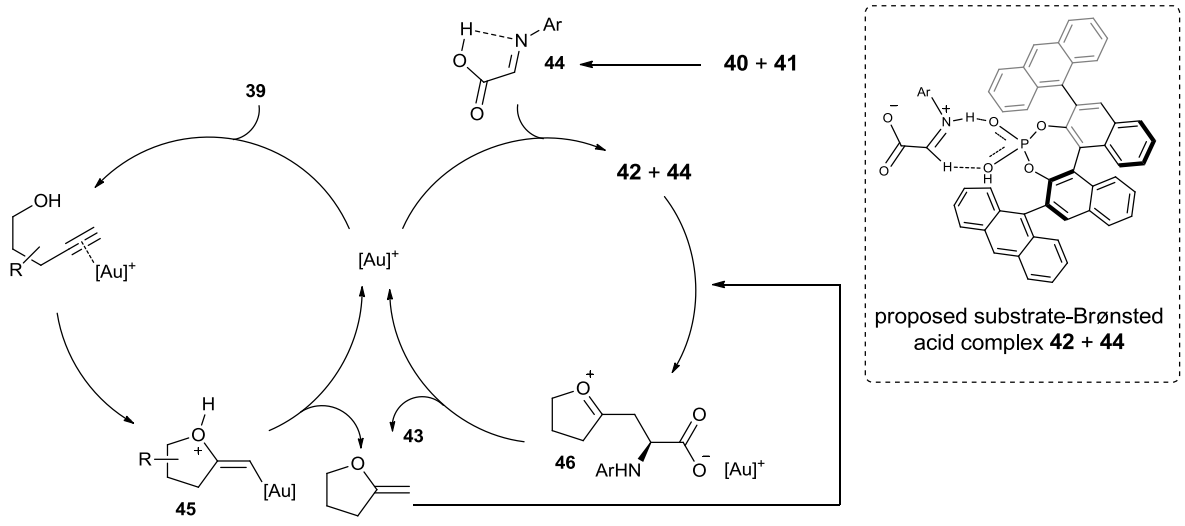
Scheme 14. Proposed origin of stereoselectivity in three component cascade

Independently, Rodriguez *et al.*[16] prepared a series of enantioenriched 5,5- and 5,6-spiroketals **43** containing masked α-amino acid moieties (Scheme 15). The reaction united three components, alkynol **39**, glyoxylic acid **40**, and arylamine **41**, and was catalysed using a combination of a Au(I) complex with a bulky chiral phosphoric acid **42**.



Scheme 15. Multicomponent coupling/spiroketalisation cascade

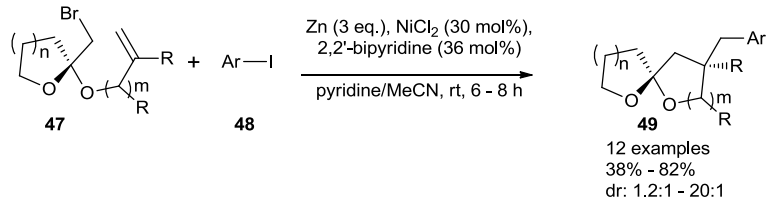
The reaction is proposed to follow a similar mechanism to the three component system developed by Gong *et al.*,[15] the principal difference being the use of glyoxylic acid **40** as the aldehyde component (Scheme 16). The glyoxylate iminium species **44** generated *in situ* may form a complex with chiral phosphoric acid **42**, providing the active chiral species to react with the enol ether **45**. Initial attack by enol ether **45** sets up the first chiral centre α to the glyoxylate in the intermediate five membered oxonium ion **46**. Importantly, the use of glyoxylate in this reaction results in spiroketal lactone products, expanding the strategic application of this methodology.



Scheme 16. Proposed reaction mechanism for alkynol, arylamine, glyoxylic acid coupling/cyclisation cascade

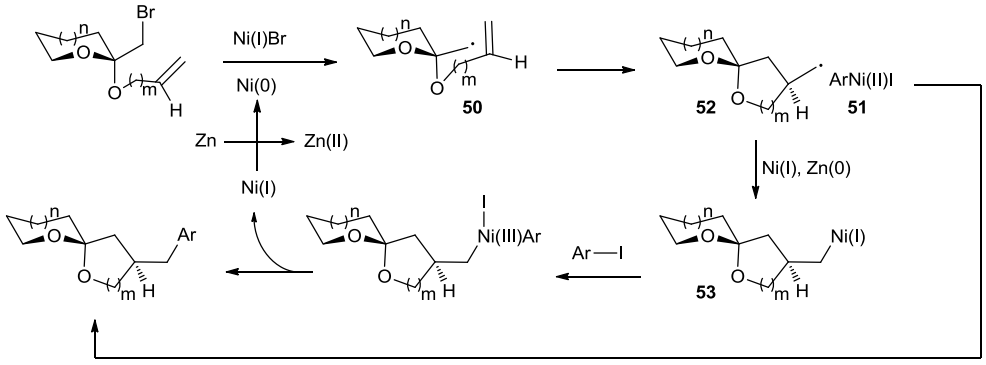
While the majority of spiroketalisation strategies focus on the formation of C-O bonds, there are an increasing number of examples where the spiroketal rings are constructed through C-C bond formation. Peng *et al.*[17] employed a Zn/Ni catalytic system to form the carbon-carbon bond of

spiroketal **49** from 6-bromo alkene **47** in which both C-O bonds have already been formed, in tandem with cross-coupling to aryl iodide **48** (Scheme 17).



Scheme 17. Zinc/nickel mediated cyclisation-coupling reaction

A radical mechanism is proposed for the reaction involving a Ni(I) catalyst and excess zinc metal (Scheme 18). The terminal alkene of the initial radical intermediate **50** may adopt a pseudo-chair conformation which may direct the diastereoselectivity of the reaction. The authors proposed that direct reaction of an *in situ* generated aryl nickel species **51** with radical **52** may provide the product. Alternatively oxidative addition of the aryl iodide with nickel species **53** and subsequent reductive elimination may be the key coupling step. Depending on the substrate, excellent diastereomeric ratios and yields were achieved.

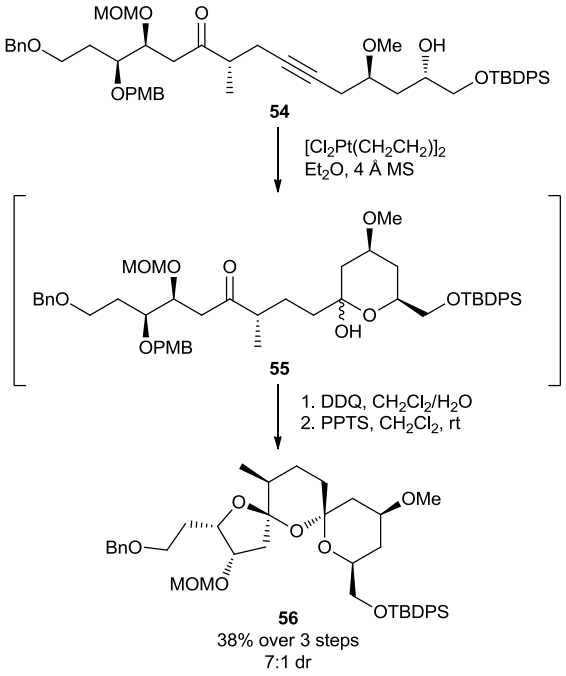


Scheme 18. Proposed mechanistic pathways to Ni/Zn radial cyclisation-coupling procedure

5. Metal-Catalysed Synthesis of Spiroketal-Containing Natural Products

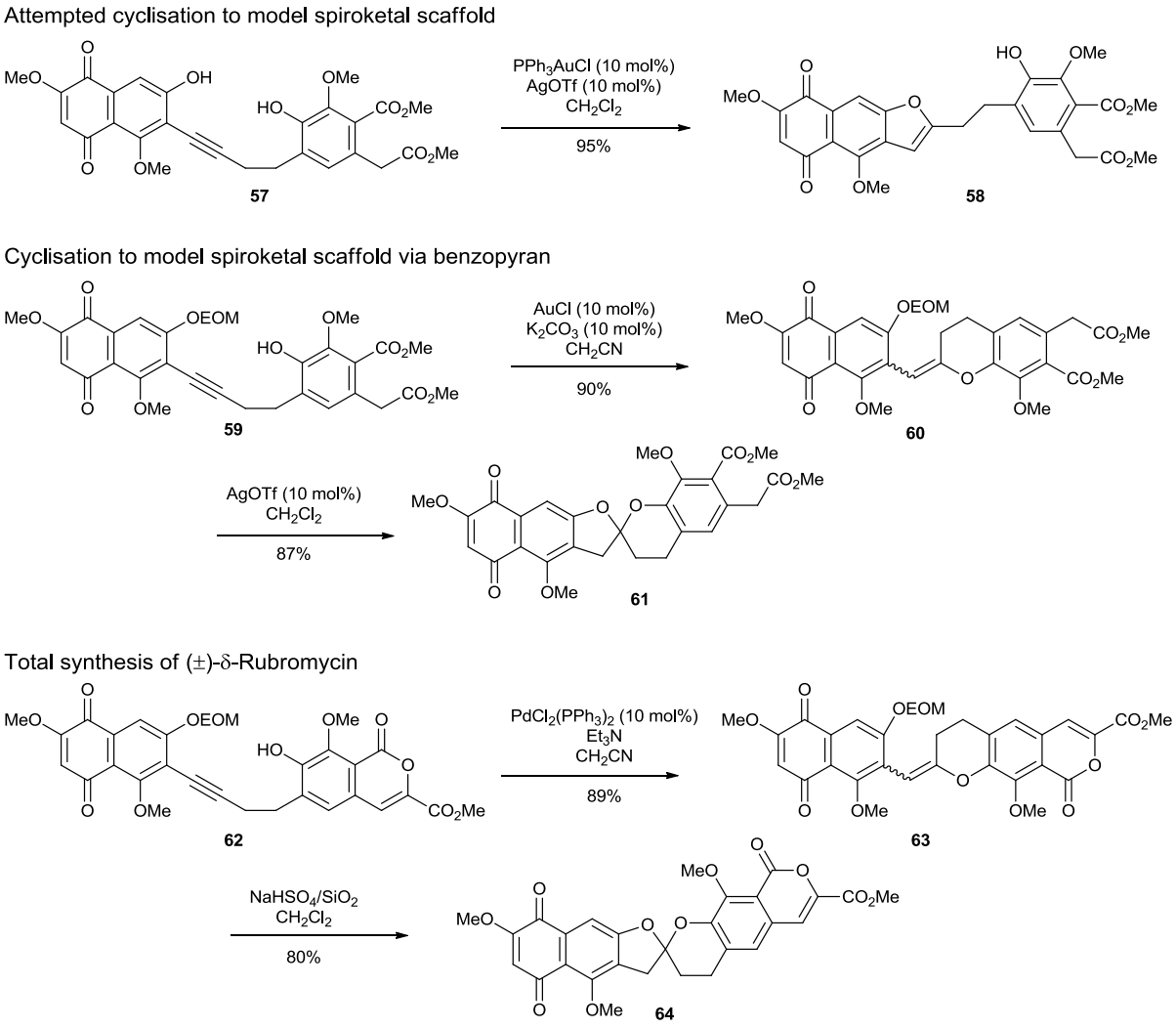
The power of these transition metal-catalysed spiroketalisations is shown in the total syntheses of several complex natural products. Recent examples include the synthesis of spirastrellolide B, rubromycin, acortatarin A and cephalosporolides E and F.

Smith *et al.*[18] employed Pt(II) catalysts in the synthesis of spirastrellolide B to access the desired hydration product of alkynol **54**, followed by a deprotection/cyclisation sequence to generate the bis-spiroketal core (Scheme 19). Attempts to form spiroketal **56** by hydroalkoxylation with AuCl were unsuccessful and cyclisation to hemiacetal **55** was necessary, followed by deprotection and cyclisation to afford the spiroketal **56**.



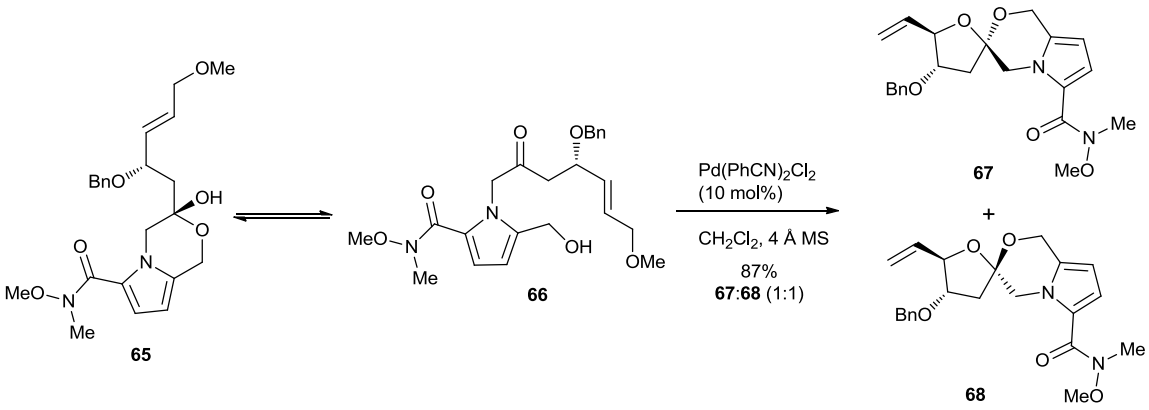
Scheme 19. Pt-Catalysed spiroketalisation towards spirastrellolide B

In 2013, Li *et al.*[19] reported a metal-catalysed cyclisation to synthesise (±)-δ-rubromycin (Scheme 20). Initial model studies revealed that attempted cyclisation of dihydroxyalkyne **57** led to the competing elimination product, benzofuran **58**. With this in mind, naphthoquinone-phenol **57** was protected as an EOM-ether **59**, prior to formation of benzopyran **60** using AuCl/K_2CO_3. Subsequent treatment with AgOTf afforded the desired spiroketal **61**. Unfortunately, when this AuCl/K_2CO_3 protocol was attempted on the rubromycin precursor **62**, spiroketalisation did not occur. Serendipitously, cyclisation was observed during the Sonogashira coupling to access **62**. Alkynol **62** was therefore subjected to the Sonogashira coupling conditions, providing benzopyran **63** in 89% yield. Deprotection/cyclisation with $NaHSO_4$/SiO_2 then afforded the desired spiroketal **64**.



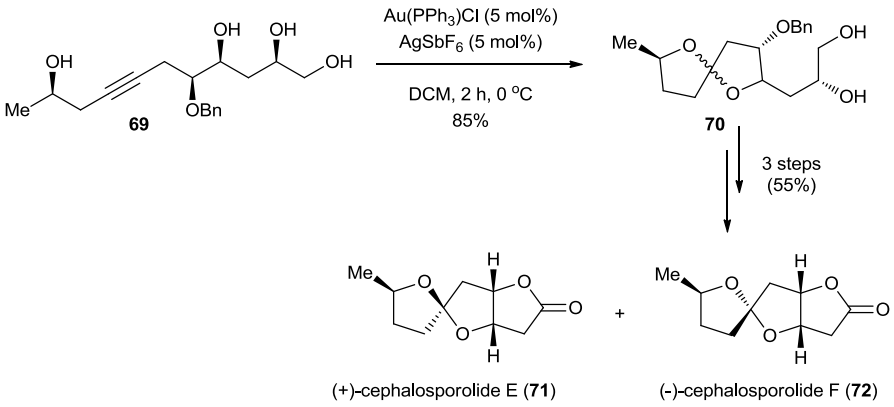
Scheme 20. Metal-catalysed cyclisation studies towards (±)-δ-rubromycin

Aponick *et al.*[3] utilised $Pd(PhCN)_2Cl_2$ to catalyse the cyclisation of hydroxyketone **66** to acortatarin A precursor **67** and its epimer **68** (Scheme 21). Alkoxypalladation and subsequent elimination afforded the spiroketal products as a 1:1 diastereomeric mixture. The poor stereoselectivity may have been due to the equilibrium between hydroxyketone **66** and cyclic hemiketal **65**.



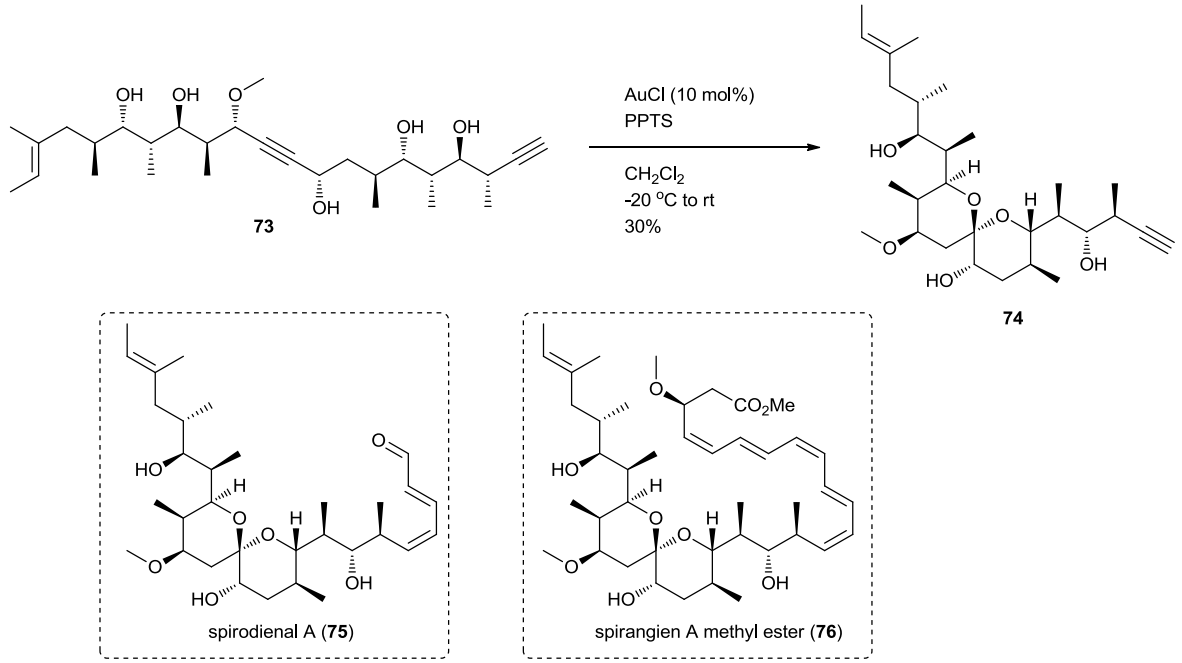
Scheme 21. Synthesis of acortatarin A utilising Pd catalysis by Aponick *et al.*

Ramana *et al.*[20] completed the total synthesis of cephalosporolides E (**71**) and F (**72**) performing the spiroketalization step in the presence of multiple unprotected hydroxyl groups (Scheme 22). Having had limited success with Pd[MeCN]Cl_2, spirocyclisation was finally achieved using the well-known Au(PPh)$_3$Cl/$AgSbF_6$ catalytic system, providing an inseparable mixture of spiroketal epimers **70**. This epimeric pair was carried through the synthesis to afford (+)-cephalosporolide E (**71**) and (-)-cephalosporolide F (**72**).



Scheme 22. Total synthesis of cephalosporolide E (**71**) and F (**72**)

Most recently, Ley *et al.*[21] utilized AuCl in the presence of PPTS to form the 6,6-spiroketal core of spirodienal A (**75**) and spirangien A methyl ester (**76**). The successful spiroketalisation of **73**, which contains multiple unprotected hydroxy groups, extensive chirality, and a non-participating terminal alkyne, demonstrates the utility of transition metals in the spiroketalization of highly complex substrates.



Scheme 23. Total synthesis of spirodienal A (**75**) and spirangien A methyl ester (**76**)

Gold(I) chloride catalysed spirocyclisation and PPTS mediated epimerisation provided the thermodynamically favoured spiroketal **74** in 30% yield. In addition to the desired spiroketal, an unsaturated 6,6-spiroketal resulting from the elimination of the methoxy ether was isolated.

6. Conclusion

The breadth and scope of the reagents, strategies, and catalytic protocols employed in this field continue to develop rapidly. Transition metal-catalysed spiroketalisations are increasingly used as mild methods for the late stage installation of spiroketal moieties in complex natural product syntheses. It would be unsurprising to see this trend continue as stereoselective methodologies are refined and their use adopted by the synthetic community. Furthermore, novel C-C disconnections are providing additional flexibility in the synthesis of spiroketals enabling facile access to previously challenging molecular structures. Future refinement of these approaches is expected to afford greater stereocontrol over spiroketal formation and the application of the more complex catalytic systems to elegant natural product syntheses.

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