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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. Spiroketales 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).
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.\textsuperscript{4,5}

The utilisation of transition metals for the synthesis of spiroketals has attracted significant attention. In particular, Pd\textsuperscript{II}, Pt\textsuperscript{II}, Au\textsuperscript{I} and Re\textsuperscript{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).
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, 1,3-enedyne diols were efficiently cyclised in the presence of a myriad of different transition metals to produce unsaturated 5,6-spiroketalts (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 2. Transition metal catalysed spiroketalisation from a range of precursors

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-spiroketalts 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-spiroketalts 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-spiroketalts 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](image)

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\textsuperscript{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-spiroketal 11 (Scheme 5).

\begin{align*}
\text{Scheme 5. Spiroketalisation/dehydration in surfactant containing aqueous media}
\end{align*}

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\textsubscript{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.\textsuperscript{9} has reported the selective preparation of 5,7-spiroketal 13 using the Co\textsubscript{2}(CO)\textsubscript{6}-alkyne complex of \(\alpha\)-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.

\begin{align*}
\text{Scheme 6. 5,7-Selective spiroketalisation via a Nicholas reaction}
\end{align*}

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 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.

Our own recent exploration 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.
Table 1. Asymmetric gold-catalysed spirocyclisation

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>L</th>
<th>AgX</th>
<th>yield</th>
<th>er (17)</th>
<th>er (18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AuPPh₃Cl</td>
<td>(R)-MeO-BIPHEP</td>
<td>AgSbF₆</td>
<td>76</td>
<td>83:17</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>AuPPh₃Cl</td>
<td>(R)-MeO-BIPHEP</td>
<td>AgSbF₆</td>
<td>96</td>
<td>94:6</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
<td>Ag(S)-TRIP</td>
<td>29</td>
<td>68:32</td>
<td>53:47</td>
</tr>
<tr>
<td>4</td>
<td>AuPPh₃Cl</td>
<td>-</td>
<td>Ag(S)-TRIP</td>
<td>81</td>
<td>88:12</td>
<td>54:46</td>
</tr>
<tr>
<td>5</td>
<td>AuCl·SMe₂</td>
<td>(S)-SEGPHOS</td>
<td>Ag(S)-TRIP</td>
<td>99</td>
<td>93:7</td>
<td>53:47</td>
</tr>
<tr>
<td>6</td>
<td>AuCl·SMe₂</td>
<td>(R)-DTBM-SEGPHOS</td>
<td>Ag(S)-TRIP</td>
<td>99</td>
<td>68:32</td>
<td>53:47</td>
</tr>
</tbody>
</table>

All reactions carried out in CH₂Cl₂ at rt. ¹¹0 mol % catalyst. ² Catalyst to L (2:1). ³[M] to AgX (1:1. ⁴ isolated yield (%) of regioisomeric mixture. ⁵ Determined by ¹H NMR. ⁶ er determined by chiral HPLC. ⁷ 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](image)

In the palladium-catalysed heterocyclisation of dihydroxyketones to synthesise 6,6-spiroketal reported by Hirai et al.,¹³ attack of the carbonyl group by the alcohol generates a hemiketal intermediate which in turn undergoes S₅₂ 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 $\sigma^*$ 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\textsuperscript{14} have utilised ‘bimetallic relay catalysis’ to synthesise a series of spiroketal and spiroaminals. A series of unsaturated keto-esters 27 were coupled and cyclised with alkynol 28 in the preparation of 5,6-spiroketal 29 (Scheme 11). The reactions proceeded with excellent diastereoselectivity with only the \textit{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 \textit{via} kinetically favoured 5-exo attack onto the triple bond. This generates nucleophile 30 \textit{in situ} which then reacts with the electrophilic $\alpha,\beta$-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\textsuperscript{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-spiroketalts 35 were obtained in high yields with good stereoselectivity (Scheme 13).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme13.png}
\caption{Scheme 13. Three component coupling/spiroketalisation cascade}
\end{figure}

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.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme14.png}
\caption{Scheme 14. Proposed origin of stereoselectivity in three component cascade}
\end{figure}

Independently, Rodriguez et al.\textsuperscript{16} prepared a series of enantioenriched 5,5- and 5,6-spiroketalts 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.
The reaction is proposed to follow a similar mechanism to the three component system developed by Gong et al., 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.

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. 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 \textit{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.\textsuperscript{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.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_19.png}
\caption{Pt-Catalysed spiroketalisation towards spirastrellolide B}
\end{figure}

In 2013, Li et al.\textsuperscript{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\textsubscript{2}CO\textsubscript{3}. Subsequent treatment with AgOTf afforded the desired spiroketal 61. Unfortunately, when this AuCl/K\textsubscript{2}CO\textsubscript{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\textsubscript{4}/SiO\textsubscript{2} then afforded the desired spiroketal 64.
Aponick et al.\textsuperscript{3} utilised Pd(PhCN)\textsubscript{2}Cl\textsubscript{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.

Ramana et al.\textsuperscript{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\textsubscript{2}, spirocyclisation was finally achieved using the well-known Au(PPh)\textsubscript{3}Cl/AgSbF\textsubscript{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).

Most recently, Ley et al.\textsuperscript{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.
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 spiroketalts 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.
References


