Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

ARTICLE

Enantioselective Synthesis of Spiroacetals: The Conquest of a Long-Sought Goal in Asymmetric Catalysis

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

Lara Cala,[a] Francisco J. Fañanás,*[a] and Félix Rodríguez*[a]

This perspective article briefly outlines the very few and recent methods reported in the bibliography on catalytic asymmetric synthesis of spiroacetals from achiral substrates.

Introduction

Spiroacetals are one of the most ubiquitous structural motifs found in nature, and they are a fundamental constituent of a number of natural products displaying biological activity.[1] Illustrative examples are shown in Figure 1 and include simple molecules such as the parent 6,6-spiroacetal olean, a sex pheromone of the olive fruitfly,[2] or complex structures containing one (berkelic acid)[3] or several spiroacetal units (spirastrellolide F)[4] in their structures.

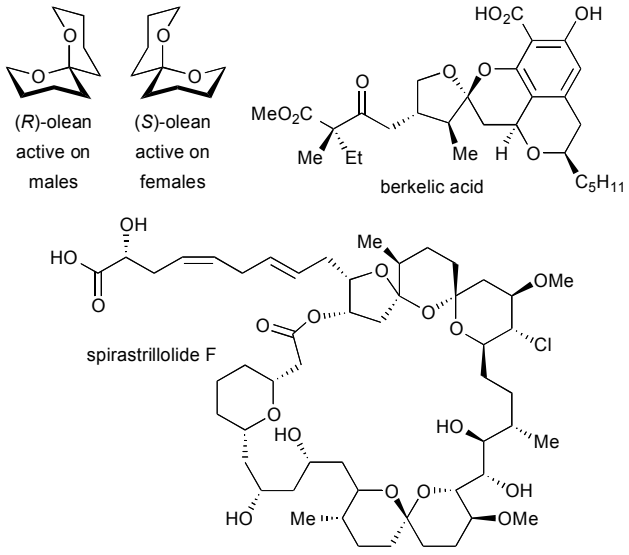
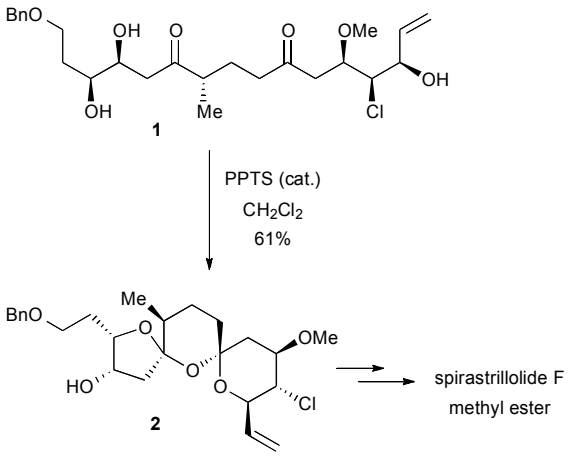


Figure 1. Natural products containing spiroacetal frameworks

The spiroacetal scaffold is in most cases essential for the bioactivity of these products and in fact, it has been shown that simplified spiroacetals derived from natural products retain biological activity similar to the parent natural product.[5] Thus, spiroacetals are considered privileged structures in drug discovery.[6] The recurring bioactivity found in spiroacetal-containing molecules could be attributed to the rigidity of this scaffold that offers precise orientation of the substituents to interact in complex biochemical systems. For this reason, the stereochemical control is a very important issue when attempting the construction of a spiroacetal framework. Particularly, the enantioselective synthesis of spiroacetals has represented an important challenge for synthetic chemists. The traditional synthetic methods to get enantiopure spiracetals relied on the use of enantiopure starting materials.[7] Thus, the stereocenters of the starting material determine the stereochemistry of the spirocyclization reaction. A typical example of these diastereoselective spiroacetalization reactions to get enantioenriched spiroacetals is shown in Scheme 1. This reaction is part of the monumental total synthesis of spirastrellolide F methyl ester published by A. Fürstner and col.[8] As shown, the northern fragment of this molecule could be easily generated by bis-spirocyclization of trihydroxy diketone **1** to give, as the major isomer, the desired product **2** in 61 % yield.



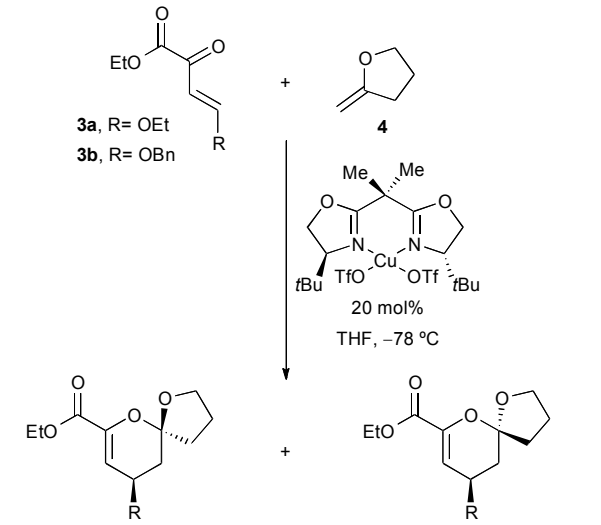
Scheme 1. Substrate-controlled synthesis of a bis-spiroacetal

Apart from these conventional substrate-controlled strategies, some success has been achieved in the synthesis of enantiopure spiroacetals by using chiral auxiliary approaches.[9] However, a much more challenging goal is the enantioselective synthesis of spiroacetals from achiral starting materials. Thus, it was not till the year 2012 when several groups, making use of modern concepts in asymmetric synthesis, offered elegant solutions to this problem. Thus, the aim of this article is to provide up to date information to the readers about the most relevant works reported in the field of catalytic asymmetric synthesis of spiroacetals.[10]

Pioneering results on catalytic asymmetric synthesis of spiroacetals

Asymmetric Cu(II)-catalyzed hetero-Diels-Alder reaction (Jørgensen)

K. A. Jørgensen and col. reported in 2000 an enantioselective inverse-demand hetero-Diels-Alder reaction of α,β-unsaturated carbonyl compounds with different electron-rich alkenes catalyzed by copper(II) complexes containing a chiral bisoxazoline-derived ligand.[11] In two particular examples these authors used as the electron-rich alkene the exocyclic enol ether **4**. Thus, the reaction of this dienophile with unsaturated keto esters **3a,b** as the heterodiene counterparts led to the formation of spiroacetals **5a,b** as mixtures of the corresponding *endo* / *exo* diastereoisomers with moderate to high enantioselectivities.



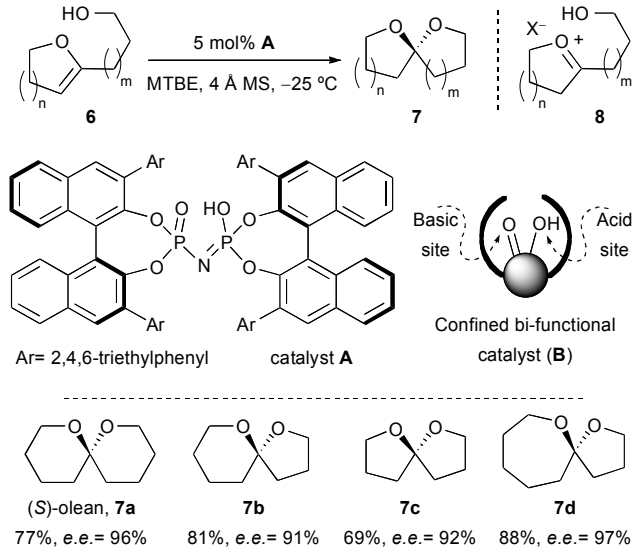
Scheme 2. Cu(II)-catalyzed asymmetric hetero-Diels-Alder reaction

The hetero-Diels-Alder reaction is an excellent strategy to get spiroacetals in a convergent way.[12] However, as far as we know, the catalytic asymmetric version of this reaction shown in Scheme 2 remains as the only example reported till now to get spiroacetals in an enantioselective way from achiral substrates. Although the scope of this reaction was not extensively studied it may be considered as the first catalytic asymmetric synthesis of spiroacetals.

Asymmetric spiroacetalizations catalyzed by chiral phosphoric acid derivatives

Spiroacetalization of cyclic enol ether derivatives with chiral binol-based C_2-symmetric imido-diphosphoric acids as catalysts (List)

In 2012, I. Čorić and B. List reported the enantioselective cycloisomerization of appropriately substituted cyclic enol ethers **6** to give the corresponding spiroacetal derivatives **7** (Scheme 3).[13] These reactions, which proceed through the formation of an oxonium intermediate **8**, require a Brønsted acid as catalyst. In this particular case, the use of a chiral binol-based C_2-symmetric imido-diphosphoric acid (**A**) leads to a geometric situation in which the subsequent intramolecular addition of the hydroxy-group in **8** occurs preferentially by one face of oxonium ion. The extremely sterically demanding chiral environment around the bifunctional active site of these catalysts is reminiscent of the deep binding pocket of enzymes (see **B** in Scheme 3). This geometrically constrained nature of the catalyst allowed the enantioselective spirocyclization of exceptionally challenging starting materials such as the enol ethers **6**. As shown, [6,6]-, [6,5]-, [5,5]-, and [7,5]-spiroacetals are easily obtained in high yields and enantioselectivities. The synthesis of the pheromone olean (**7a**) in enantiopure form represents an impressive example of the power of these catalysts.

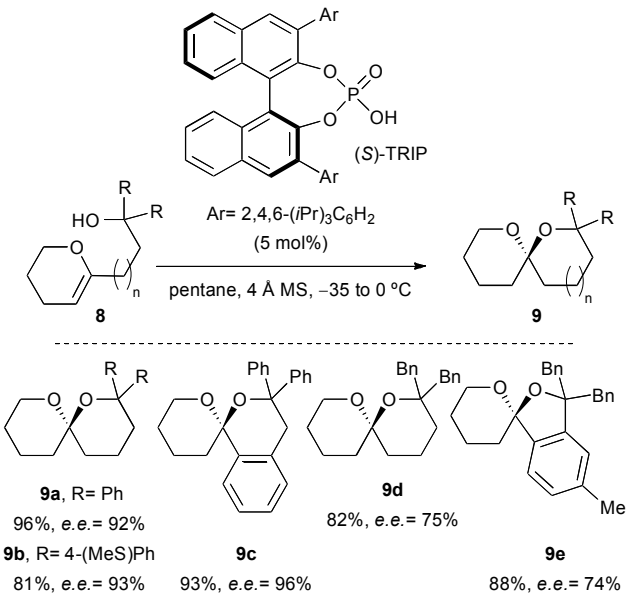


Scheme 3. Enantioselective spiroacetalization catalyzed by an imido-diphosphoric acid derivative

Spiroacetalization of cyclic enol ether derivatives with simple chiral binol-derived phosphoric acid as catalysts (Nagorny)

In a study developed almost at the same time than the above commented B. List´s work, P. Nagorny and col. demonstrated that high levels of enantiocontrol could be achieved in the spirocyclization reaction of tertiary alcohols **8** by using the less sophisticated and commercially available binol-derived phosphoric acid catalyst TRIP in pentane as solvent (Scheme 4).[14] The highest enantioselectivities were observed for diaryl-

substituted compounds (**9a-c**) while the enantioselectivities were lower for less rigid dibenzyl-substituted products (**9d,e**).

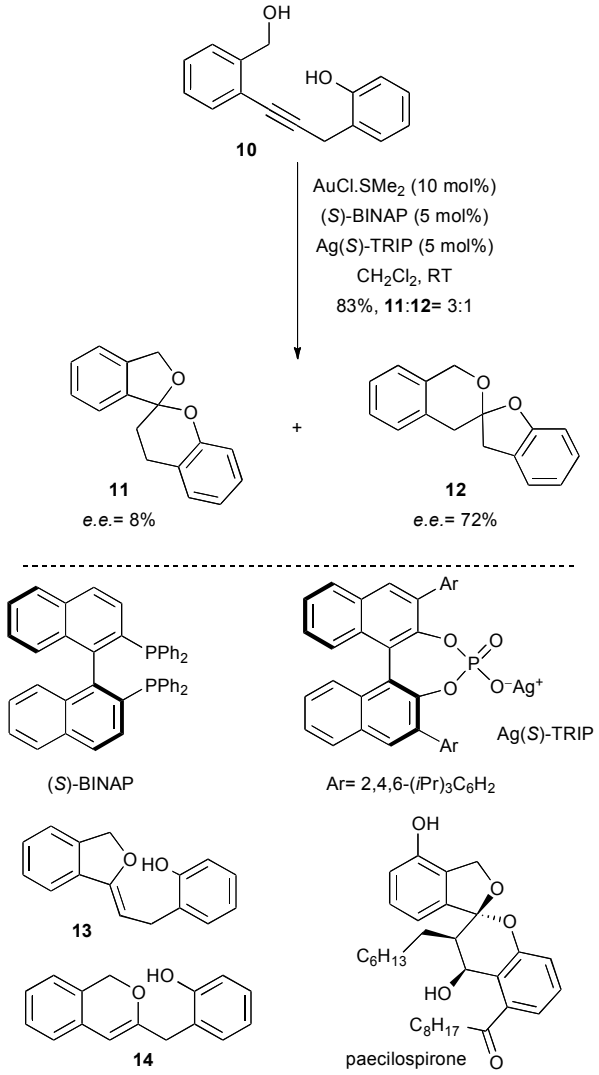


Scheme 4. Enantioselective spiroacetalization catalyzed by TRIP

Spiroacetalization of alkyndiol derivatives with chiral gold phosphates as catalysts (Brimble)

M. A. Brimble and col. recently reported their attempts to perform the stereoselective spiroacetalization of alkyndiol derivative **10** under different gold-catalysis conditions (Scheme 5).[15] A regioisomeric mixture of spiroacetals **11** and **12** was obtained independently on the catalytic system used. Formation of this mixture is easily explained considering that the reaction proceeds through the initial coordination of the gold complex to the alkyne. This coordination favours an unselective intramolecular addition of the benzylic alcohol to the activated triple bond to give the corresponding endocyclic (**13**) or exocyclic (**14**) enol ether. These enol ethers are the direct precursors of the final spiroacetals **11** and **12**. Regarding the enantioselectivity of the process, the best results were reached by using as catalyst the chiral gold (I) complex derived from (*S*)-BINAP in the presence of the chiral silver phosphate derived from (*S*)-TRIP [Ag(*S*)-TRIP]. However, very low enantioselectivity was observed for spiroacetal **11** (*e.e*= 8%) and moderate for spiroacetal **12** (*e.e*= 72%).

Interestingly, the structure of the major isomer of this reaction (**11**) resembles the skeleton of the natural product paecilospirone (Scheme 5). Unfortunately, almost no asymmetric induction was observed in the formation of this isomer. Although, this result limits the applicability of this strategy for the synthesis of paecilospirone, many other metallic complexes have been found to be able to promote the spiroacetalization of alkyndiols and then, better regio- and enantioselectivities could be found by using other chiral catalysts.[16]



Scheme 5. Stereoselective spiroacetalization of an alkyndiol

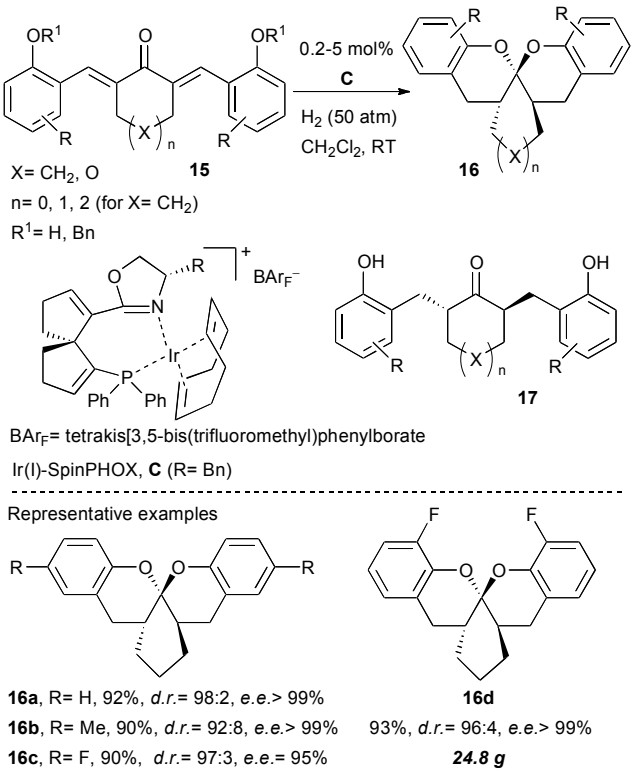
Enantioselective modification of enone derivatives and further spiroacetalization

Asymmetric Ir(I)-catalyzed hydrogenation of dienone derivatives (Ding)

In 2012, K. Ding and col reported a wise strategy to get enantiopure spiroacetals from simple dienone derivatives (Scheme 6).[17] Based on their own experiences with iridium(I)-catalyzed hydrogenations, these authors studied the catalytic asymmetric hydrogenation of dienone derivatives **15**, followed by a diastereoselective cyclization to get the aromatic spiroacetals **16**. Very high diastereo- and enantioselectivities were observed by using the chiral Ir(I)-SpinPHOX catalyst **C** (R= Bn).

This transformation proceeds through the initial enantioselective reduction of the prochiral dienone **15** (with concomitant benzyl-deprotection when R^1= Bn) to the chiral trans-2,6-disubstituted cyclohexanone **17**, followed by a highly diastereoselective spirocyclization. This reaction provides

excellent results for cyclic ketone derivatives **15**. However, for those ketones without a cyclic backbone, the reaction proceeds without asymmetric induction with only racemic material obtained.

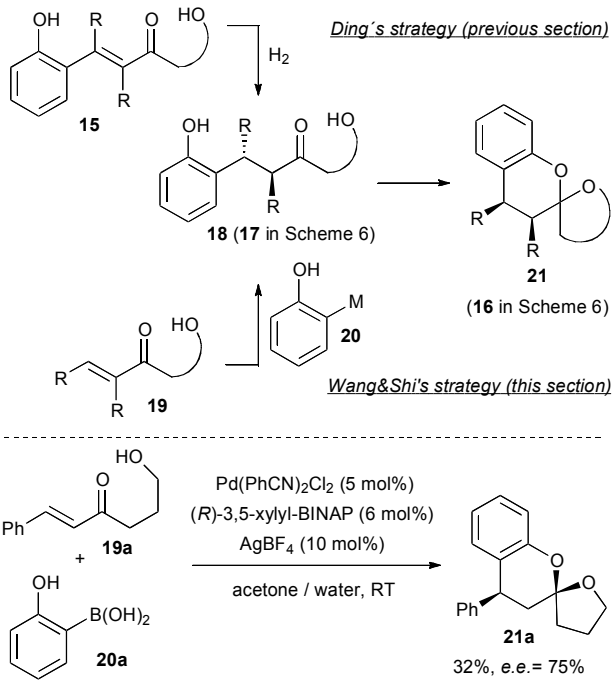


Scheme 6. Enantiopure spiroacetals from dienones by asymmetric hydrogenation

This reaction has been performed at multigram scales without problems.[17b] For example, 24.8 grams of compound **16d** were easily obtained in one batch by using just 0.2 mol% of chiral catalyst **C**. Interestingly, compound **16d** served as precursor of potentially very useful spiroketal-based diphosphine (SKP) ligands.[18]

Asymmetric Pd(II)-catalyzed Michael-type addition to an enone derivative (Wang & Shi)

The key point for the successful Ding's asymmetric synthesis of spiroacetals described in the previous section was the asymmetric generation of intermediate **17** through a hydrogenation reaction (see Schemes 6 and 7). This dihydroxyketone derivative **17** (or **18** in Scheme 7) easily evolves to the final enantiopure spiroacetal **16** (or **21**) through a diastereoselective cyclization. F. Wang, M. Shi and col. further extended this concept by proposing a different way to get the key intermediates **18** (Scheme 7).[19] Thus, a simple asymmetric Michael-type addition of an appropriate hydroxy-substituted arene **20** to an enone **19** would render the dihydroxyketone derivative **18** and finally the spiroacetals **21** in an enantioselective way. It should be noted that this concept was mainly exploited for the enantioselective synthesis of [3.3.1]-bicyclic acetals.[19] However, a single example about the asymmetric synthesis of spiroacetals by this approach is reported in this work. Specifically, the reaction of enone derivative **19a** with the boronic acid **20a** in the presence of $Pd(PhCN)_2Cl_2$ (5 mol%), (*R*)-3,5-xylyl-BINAP (6 mol%) and $AgBF_4$ (10 mol%) in a mixture of acetone and water afforded the spiroacetal **21a** in low yield (32%) and moderate enantioselectivity (75%).



Scheme 7. Enantiopure spiroacetals from an enone derivative by asymmetric Michael-type addition of a boronic acid

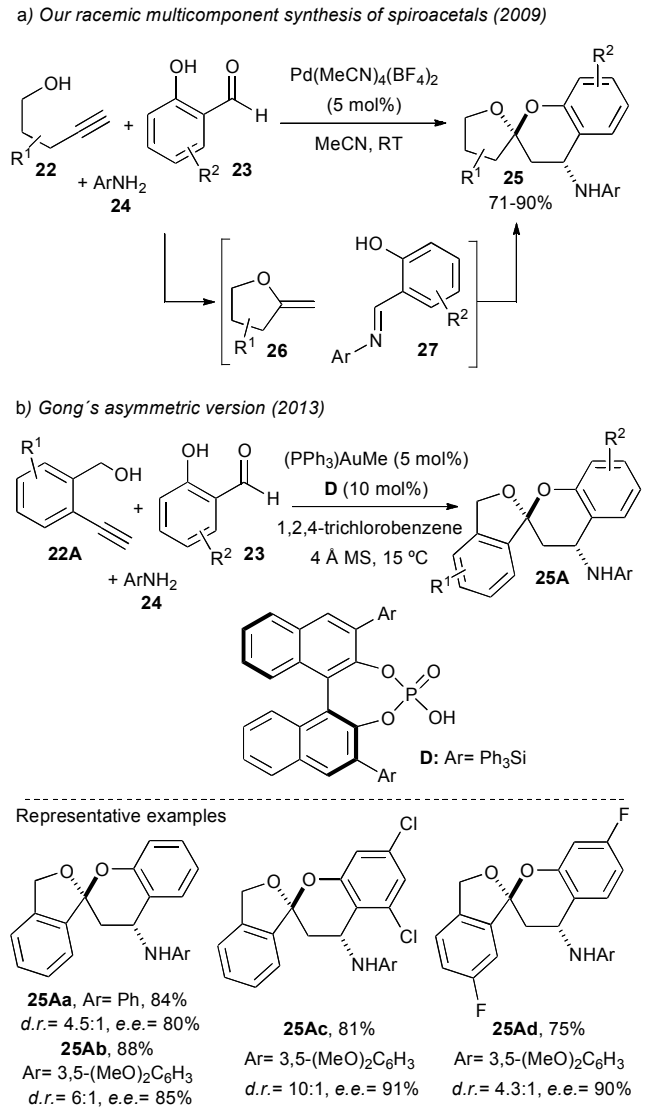
Catalytic asymmetric synthesis of spiroacetals by multicomponent coupling reactions

Asymmetric gold / chiral phosphoric acid catalyzed synthesis of chroman spiroacetals (Gong)

In 2009, our group reported a new diastereoselective palladium(II) catalyzed synthesis of chroman spiroacetals **25** through a one-pot, three-component coupling reaction of alkynols **22**, salicylaldehydes **23** and anilines **24** (Scheme 8).[20] The reaction is believed to proceed through the formation of two intermediates, the exocyclic enol ether **26** and the imine **27**. The subsequent coupling reaction between these two reagents by a formal Mannich-type addition followed by spiroacetalization leads to the final products **25**. Interestingly, we have applied a modified version of this reaction in the key step of a straightforward total synthesis of the natural product berkelic acid.[21]

Also, L.-Z. Gong and col. developed an asymmetric version of this process by using a chiral catalytic system formed by $(PPh_3)AuMe$ (5 mol%) and the BINOL-derived phosphoric acid **D** (10 mol%).[22] Thus, the reaction of alkynol derivatives **22A**, salycilaldehydes **23** and anilines **24** led to chroman spiroacetals **25A** in good yield, variable diastereoselectivity (*d.r.* from >25:1 to 3:1) and high enantioselectivity (*e.e.*= 69-95%). In this reaction, a gold phosphate is formed in situ from $(PPh_3)AuMe$

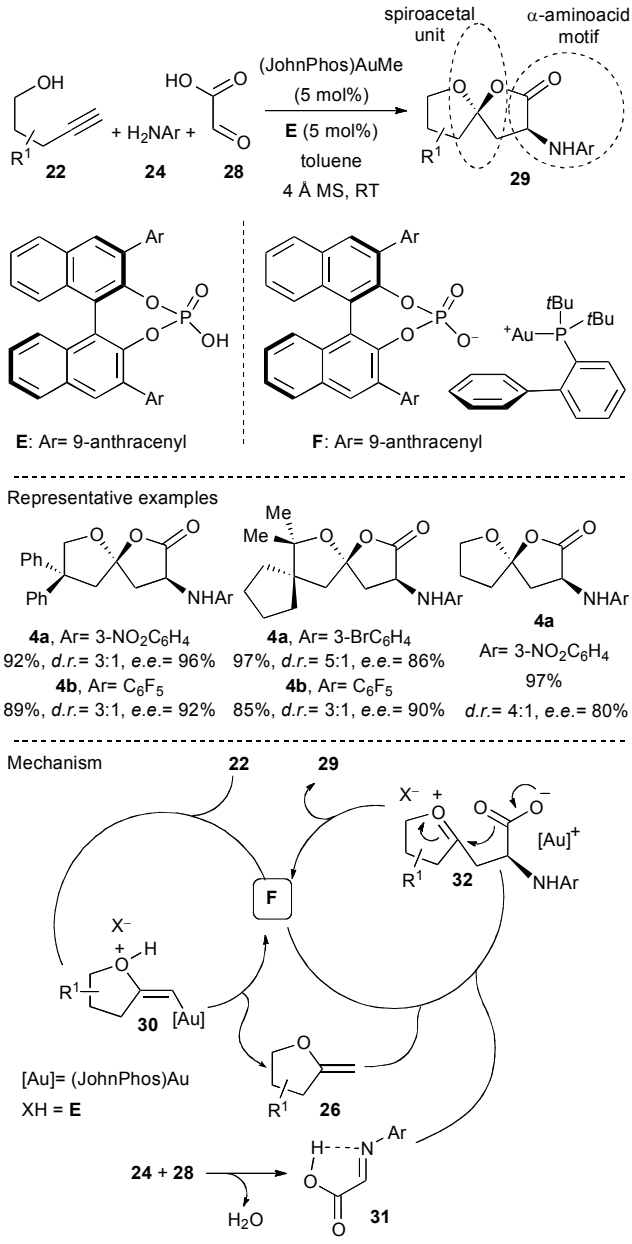
and **D**. Formation of the enol ether intermediate **26** is catalysed by this gold phosphate. In the other hand, the remaining chiral phosphoric acid **D** coordinates to the imine intermediate **27** favouring an asymmetric Mannich-type reaction with enol ether **26**. The subsequent diastereoselective spirocyclization affords the spiroacetals **25A**. In contrast to the racemic version above commented, this asymmetric reaction seems to be limited to alkynol derivatives **22A** containing a benzylic primary alcohol because other substitution in alkynol **22** was not reported.



Scheme 8. Synthesis of chroman spiroacetals by a multicomponent coupling reaction

Asymmetric gold / chiral phosphoric acid catalyzed synthesis of [5,5]-spiroacetals (Our)

In parallel to the aforementioned Gong´s studies, we investigated the enantioselective gold-phosphate catalysed three-component coupling reaction between pentynol derivatives **22**, anilines **24** and glyoxylic acid **28** (Scheme 9).[23] Under the appropriate conditions involving the use of a catalytic system formed by the combination of (JohnPhos)AuMe (5 mol%) and chiral BINOL-derived phosphoric acid **E** (5 mol%) in toluene at room temperature, we were able to get the [5,5]-spiroacetals **29** in high yield and enantiomeric excess.



Scheme 9. Asymmetric synthesis of [5,5]-spiroacetals by a multicomponent coupling reaction

Interestingly, compounds **29** may be considered as hybrid molecules comprising a spiroacetal unit (natural product inspired scaffold) and an α-amino acid motif (a privileged fragment). It should also be noted that the reaction proceeds with equimolecular amounts of (JohnPhos)AuMe (5 mol%) and chiral BINOL-derived phosphoric acid **E** (5 mol%). Thus, the reaction between these two reagents leads, after releasing a molecule of methane, to the formation of the real active catalytic species, the gold phosphate **F**. This catalyst promotes

the cycloisomerization of pentynol derivative **22** to give the enol ether **26** through the intermediate **30**. The formal Mannich-type addition of this enol ether to the *in situ* formed imine **31** delivers the intermediate **32**, which upon cyclization provides the final products **29**. Interestingly, in the first catalytic cycle the main role of the catalyst is played by its cationic part, the gold(I) ion, being responsible for the activation of the alkynol **22**. Meanwhile, in the second catalytic cycle, the main role is played by the anionic part of the catalyst, the phosphate, creating the appropriate chiral environment to produce the final enantioenriched products **29**.

Conclusions

The enantioselective construction of spiroacetals from achiral substrates has remained as an unmet challenge for synthetic organic chemists until very recently. Thus, this Perspective article collects the examples reported in the literature on catalytic asymmetric synthesis of spiroacetals from achiral substrates. Although this research area is still in its infancy and just a few works have appeared, the power of the strategies so far developed in assembling very useful frameworks has been demonstrated. Also, the creativity of the authors to circumvent the inherent problems associated with the catalytic asymmetric synthesis of spiroacetals is reflected in most of the examples covered in this article. However, some challenges still remain to be fully addressed. For example, the stereoselective synthesis of spiroacetals in cases where the conformational and stereoelectronic factors prevent the formation of the desired configuration deserves further investigation.[14] We hope this compilation has provided an appropriate background for the present topic and exciting developments in the field are expected to appear in the near future.

Acknowledgements

We acknowledge financial support from MICINN of Spain (grant CTQ2010-16790), MEC (FPU-predoctoral grant to L. C.).

Notes and references

[a] Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo, Julián Clavería 8, 33006-Oviedo, Spain. Fax: (+34) 985103446; Tel: (+34) 985106224; E-mail: fjfv@uniovi.es; frodriguez@uniovi.es

1 *(a)* F. Perron and K. F. Albizati, *Chem. Rev.*, 1989, **89**, 1617-1661; *(b)* J. E. Aho, P. M. Pihko and T. K. Rissa, *Chem. Rev.*, 2005, **105**, 4406-4440; *(c)* S. V. Ley, L.-G. Milroy and R. M. Myers, Product Class 9: Spiroketals, in *Science of Synthesis*, ed. S. Warriner, Georg Thieme, Stuttgart, 2007, vol 29, p. 613; *(d)* J. A. Palmes and A. Aponick, *Synthesis*, 2012, **44**, 3699-3721.

2 G. Haniotakis, W. Francke, K. Mori, H. Redlich and V. Schurig, *J. Chem. Ecol.*, 1986, **12**, 1559-1568.

3 A. A. Stierle, D. B. Stierle and K. Kelly, *J. Org. Chem.*, 2006, **71**, 5357-5360.

4 *(a)* D. E. Williams, M. Roberge, R. Van Soest and R. J. Andersen, *J. Am. Chem. Soc.*, 2003, **125**, 5296–5297; *(b)* D. E. Williams, M. Lapawa, X. Feng, T. Tarling, M. Roberge and R. J. Andersen, *Org. Lett.*, 2004, **6**, 2607–2610; *(c)* D. E. Williams, R. A. Keyzers, K. Warabi, K. Desjardine, J. L. Riffell, M. Roberge and R. J. Andersen, *J. Org. Chem.*, 2007, **72**, 9842–9845; *(d)* K. Warabi, D. E. Williams, B. O. Patrick, M. Roberge and R. J. Andersen, *J. Am. Chem. Soc.*, 2007, **129**, 508–509.

5 See for example: *(a)* A. A. Birkbeck, S. V. Ley and J. C. Prodger, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 2637-2642; *(b)* S. Mitsuhashi, H. Shima, T. Kawamura, K. Kikuchi, M. Oikawa, A. Ichihara and H. Oikawa, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2007-2012; *(c)* F. M. Uckun, C. Mao, A. O. Vassilev, H. Huang and S. T. Jan, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 541-545; *(d)* G. Zinzalla, L.-G. Milroy and S. V. Ley, *Org. Biomol. Chem.*, 2006, **4**, 1977-2002.

6 L.-G. Milroy, G. Zinzalla, F. Loiseau, Z. Qian, G. Prencipe, C. Pepper, C. Fegan and S. V. Ley, *ChemMedChem,* 2008, **3**, 1922-1935.

7 B. R. Raju and A. K. Saikia, *Molecules*, 2008, **13**, 1942-2038.

8 *(a)* G. W. O'Neil, J. Ceccon, S. Benson, M.-P. Collin, B. Fasching and A. Fürstner, *Angew. Chem. Int. Ed.*, 2009, **48**, 9940–9945; *(b)* S. Benson, M.-P. Collin, G. W. O'Neil, J. Ceccon, B. Fasching, M. D. B. Fenster, C. Godbout, K. Radkowski, R. Goddard and A. Fürstner, *Angew. Chem. Int. Ed.*, 2009, **48**, 9946–9950.

9 *(a)* C. Iwata, K. Hattori, S. Uchida and T. Imanishi, *Tetrahedron Lett.*, 1984, **25**, 2995-2998; *(b)* C. Iwata, M. Fujita, K. Hattori, S. Uchida and T. Imanishi, *Tetrahedron Lett.*, 1985, **26**, 2221-2224; *(c)* M. Uchiyama, M. Oka, S. Harai and A. Ohta, *Tetrahedron Lett.*, 2001, **42**, 1931-1934.

10 See also: *(a)* M. Wilsdorf and H.-U. Reissig, *Angew. Chem. Int. Ed.*, 2012, **51**, 9486–9488; *(b)* P. Nagorny, Z. Sun and G. A. Winschel, *Synlett*, 2013, **24**, 661-665.

11 H. Audrain, J. Thorhauge, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2000, **65**, 4487-4497.

12 M. A. Rizzacasa and A. Pollex, *Org. Biomol. Chem.*, 2009, **7**, 1053-1059.

13 I. Čorić and B. List, *Nature*, 2012, **483**, 315-319.

14 Z. Sun, G. A. Winschel, A. Borovika and P. Nagorny, *J. Am. Chem. Soc.*, 2012, **134**, 8074-8077.

15 R. Quach, D. P. Furkert and M. A. Brimble, *Tetrahedron Lett.*, 2013, **54**, 5865-5868.

16 For the use of transition metal catalysts in the spirocyclization of alkyndiols see reference 1d.

17 *(a)* X. Wang, Z. Han, Z. Wang and K. Ding, *Angew. Chem. Int. Ed.*, 2012, **51**, 936-940; *(b)* X. Wang, P. Guo, X. Wang, Z. Wang and K. Ding, *Adv. Synth. Catal.*, 2013, **355**, 2900-2907.

18 *(a)* X. Wang, F. Meng, Y. Wang, Z. Han, Y.-J. Chen, L. Liu, Z. Wang and K. Ding, *Angew. Chem. Int. Ed.*, 2012, **51**, 9276-9282; *(b)* Z.-Y. Cao, X. Wang, C. Tan, X.-L. Zhao, J. Zhou and K. Ding, *J. Am. Chem. Soc.*, 2013, **135**, 8197-8200.

19 F. Wang, F. Chen, M. Qu, T. Li, Y. Liu and M. Shi, *Chem. Commun.*, 2013, **49**, 3360-3362.

20 J. Barluenga, A. Mendoza, F. Rodríguez and F. J. Fañanás, *Angew. Chem. Int. Ed.*, 2009, **48**, 1644-1647.

21 F. J. Fañanás, A. Mendoza, T. Arto, B. Temelli and F. Rodríguez, *Angew. Chem. Int. Ed.*, 2012, **51**, 4930-4933.

22 H. Wu, Y.-P. He and L.-Z. Gong, *Org. Lett.*, 2013, **15**, 460-463.

23 L. Cala, A. Mendoza, F. J. Fañanás and F. Rodríguez, *Chem. Commun.*, 2013, **49**, 2715-2717.

Table of Contents

This perspective article summarizes the few and recently reported methods on catalytic asymmetric synthesis of spiroacetal derivatives from achiral substrates.