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A catalytic multicomponent coupling reaction for the enantioselective synthesis of spiroacetals†

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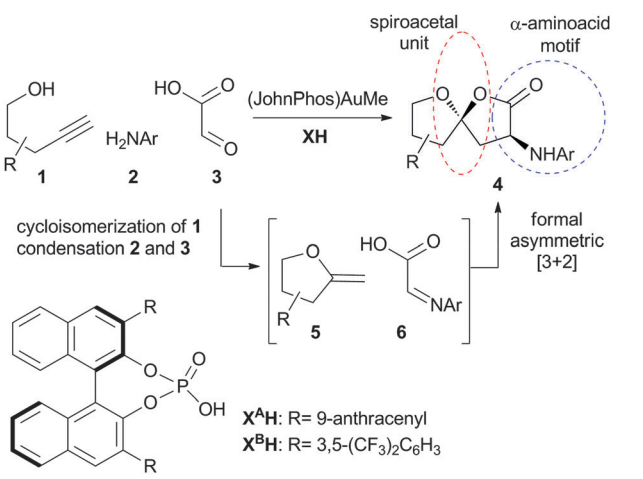
The first multicomponent catalytic asymmetric synthesis of spiroacetals has been described. Hybrid molecules comprising a spiroacetal scaffold (a natural-product inspired scaffold) and an α-amino acid motif (a privileged fragment) are easily available through a gold phosphate-catalysed one-pot three component coupling reaction of alkynols, anilines and glyoxylic acid.

Natural products are an exceptional source of drug leads and a continuous inspiration for the design of small-molecule libraries for drug discovery.[1] In this context, spiroacetals have been found as a key structural unit in many biologically active and structurally diverse natural products.[2] Interestingly, it has been shown that simplified spiroacetals derived from natural products frequently retain biological activity similar to the parent natural product.[3] Therefore, the spiroacetal framework makes an ideal candidate for the development of potentially useful natural-product-like compounds.[4] In this context, we have recently reported a new strategy for the synthesis of functionalized chroman spiroacetals,[5] which was further exploited in the total synthesis of the bioactive natural product (–)-berkelic acid.[6]

Following our interest in this field, we became particularly interested in the development of a ''reagent-controlled'' asymmetric synthesis of spiroacetals.[7] In this context, it should be stressed that despite the unquestionable interest in optically active spiroacetals, to the best of our knowledge, only three strategies for the enantioselective synthesis of these compounds from achiral substrates have been reported.[8] Thus, K. A. Jørgensen and colleagues reported a copper-catalyzed asymmetric hetero-Diels–Alder reaction where just two examples of chiral [6,5]-spiroacetals were synthesized with moderate enantioselectivity.[8a] Z. Wang, K. Ding and colleagues applied an iridium-catalyzed hydrogenation reaction for the synthesis of enantioenriched chroman [6,6]-spiroacetals.[8b] The third example has also been reported very recently by B. List and colleagues.[8c] They used a confined Brønsted acid based on a C_2-symmetric imidophosphoric acid motif to achieve catalytic enantioselective spiroacetalization of 2-hydroxyalkyl-substituted cyclic enol ethers. It should be noted that only the first example implies an intermolecular coupling process and the other two are intramolecular reactions.

Thus, the scarcity of catalytic asymmetric methods for the enantioselective synthesis of spiroacetals, and in particular the absence of asymmetric approaches to the [5,5]-spiroacetal scaffold motivated us to investigate this issue. We envisaged that the three-component coupling reaction of alkynol derivatives **1**, arylamines **2** and glyoxylic acid **3** in the presence of an appropriate chiral catalyst should lead to enantioenriched [5,5]-spiroacetal derivatives **4** (Scheme 1).[9]

We thought that the cycloisomerization reaction of alkynol derivatives **1** should deliver the exocyclic enol ethers **5**. Moreover the condensation reaction between glyoxylic acid and amines **2** should give imines **6**. Further reaction between these *in situ* formed intermediates **5** and **6** would lead to our desired



Scheme 1 Our approach for the enantioselective synthesis of spiroacetals.

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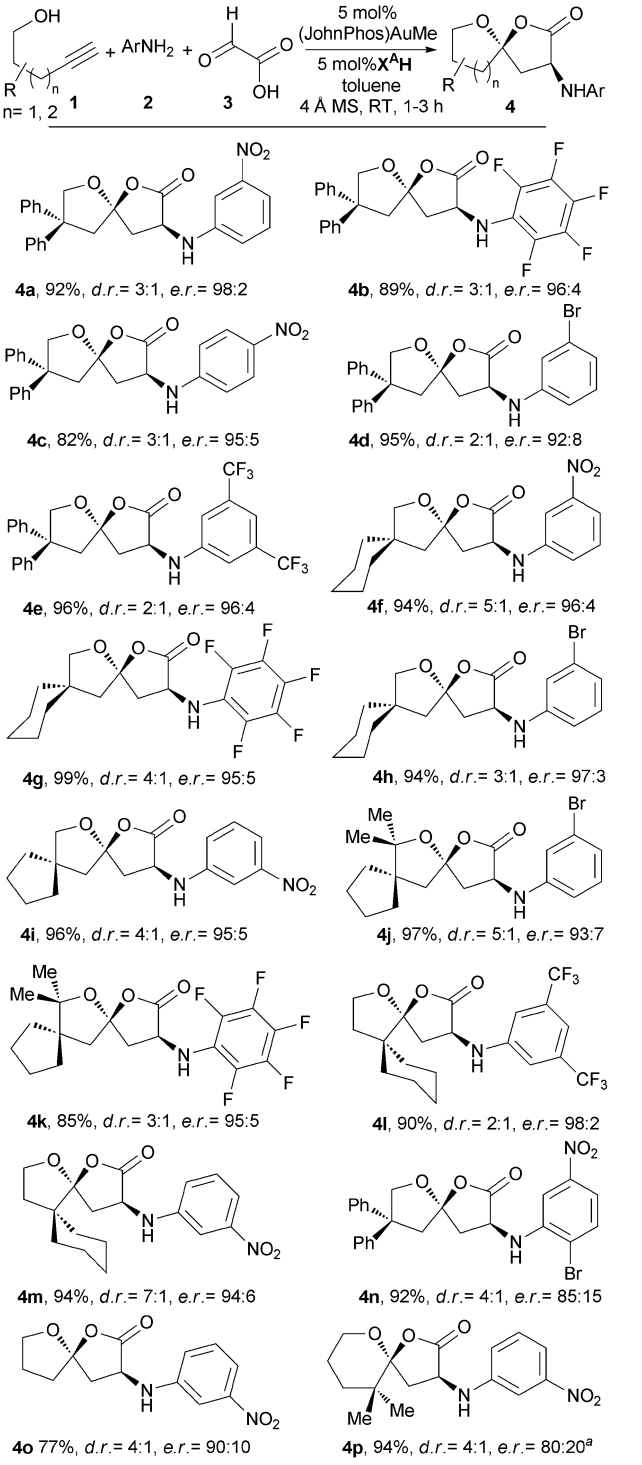
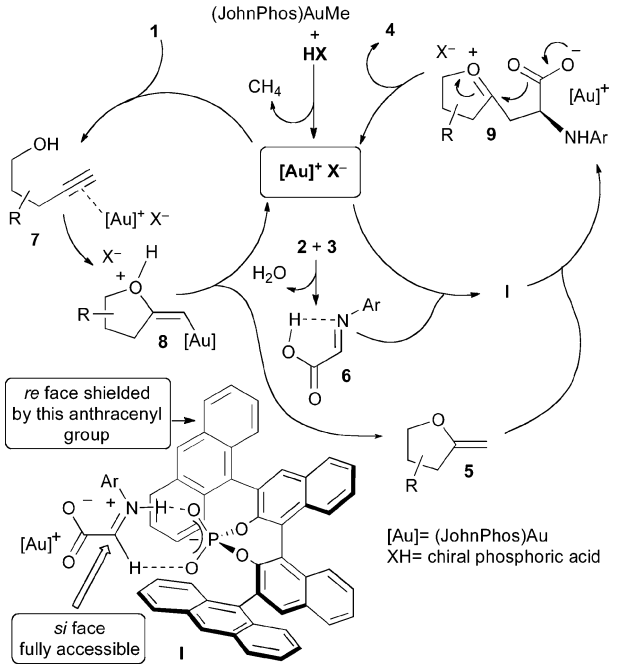
[5,5]-spiroacetal derivatives **4**. Regarding the catalyst, we thought that the combination of (JohnPhos)AuMe and a (*R*)-BINOL-derived phosphoric acid **XH** would be ideal because the cationic gold phosphate formed should be able to catalyse both the cycloisomerization of **1** to form the cyclic enol ethers **5** and the formal asymmetric [3 + 2]-cycloaddition between these enol ethers **5** and imines **6**.[10] The particular structural features of compounds **4** should be remarked. These products may be considered as hybrid molecules comprising a spiroacetal unit (a natural-product inspired scaffold) and an α-amino acid motif (a privileged fragment). The concept of combining a biologically active motif within a natural product-inspired scaffold system is very attractive because it provides compounds with enhanced structural complexity along with potential bioactivity.[11]

After a few experiments to check the feasibility of the proposed reaction (see ESI†), we found that the use of the phosphoric acid $\mathbf{X^AH}$ containing the bulky 9-anthracenyl substituents led to the best results (Scheme 1). Thus, as shown in Scheme 2, several alkynol derivatives **1**, anilines **2** and glyoxylic acid **3** were reacted in toluene as the solvent at room temperature in the presence of the phosphate gold catalyst (5 mol% (JohnPhos)AuMe/$\mathbf{X^AH}$). Under these conditions, a series of compounds **4** with diverse functionality around the central spiroacetal framework were obtained in high yield and enantioselectivity. The reaction was general in terms of the alkynol **1** used and substitution at all carbons of the chain connecting the hydroxy group and the alkyne was tolerated without erosion of efficiency and enantioselectivity. Unsubstituted 4-pentyn-1-ol could also be used in this reaction (**4o**). Anilines **2** containing an electron-withdrawing group or a halogen were appropriate coupling partners for this multicomponent reaction.[12] Furthermore, the reaction is not limited to the construction of [5,5]-spiroacetal frameworks and [6,5]-spiroacetal derivatives may be obtained when the reaction is performed with 5-hexyn-1-ol derivatives **1** (n = 2). Accordingly, compound **4p** was synthesized and isolated in very high yield (94%), with good diastereoselectivity (dr = 4 : 1) and an 80 : 20 enantiomeric ratio. Interestingly, in this case the best result was obtained by using the phosphoric acid derivative $\mathbf{X^BH}$. It should be noted that for the purpose of testing biological activity both diastereoisomers **4** and *diast*-**4** are of high interest and so we tried to isolate both. However, if required, the diastereoselectivity of the reaction may be improved by heating the reaction mixture for several hours.[13] It is also important to remark that the enantiomeric excesses of the minor diastereoisomers were very high and comparable to those observed for the major diastereoisomers (see ESI†). The absolute configuration of **4n** was determined by single-crystal X-ray analysis and the configuration of the remaining products was assigned by analogy.[14]

A plausible mechanism for the present reaction is illustrated in Scheme 3. In the first place, we propose the *in situ* generation of the active catalytic species by reaction of (JohnPhos)AuMe with the Brønsted acid **XH**. This reaction leads to the formation of the corresponding gold phosphate complex after releasing a molecule of methane. Coordination of the gold cation to the carbon–carbon triple bond of alkynol **1** produces complex **7**. This coordination favours the intramolecular *exo*-addition of the hydroxy group to the alkyne, giving rise to alkenyl–gold complex **8**. A conventional protodemetallation reaction delivers the exocyclic enol ether **5** regenerating the gold-derived catalyst. On the other hand, the condensation reaction between glyoxylic acid **3** and anilines **2** gives rise to imine **6**. We feel likely that



Scheme 2 Asymmetric synthesis of spiroacetals **4**. [a]Phosphoric acid derivative $\mathbf{X^BH}$ was used.



Scheme 3 Proposed mechanism for the formation of spiroacetals **4**.

activation of the imine **6** by formation of an intramolecular hydrogen bond and further interaction with the gold phosphate would lead to an activated species **I**.[15] Subsequent nucleophilic addition of the enol ether **5** would give the oxonium intermediates **9**, which upon cyclization would provide the final product **4** regenerating the catalyst. 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 **1**. 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 **4**.

To justify the formation of the enantiomer observed in products **4** we consider the model proposed by M. Terada and colleagues for the chiral phosphoric acid catalyzed reaction between glyoxylates and enecarbamates.[16] In this model, supported by computational studies, the key feature is the formation of a hydrogen bond between the formyl hydrogen atom and one of the oxygen atoms of the phosphoric acid. We propose a similar coordination mode that accounts for the sense of asymmetric induction observed (**I** in Scheme 3). Thus, in the double hydrogen-bonded complex formed, the enantiotopic *re* face of the imine is effectively shielded by one of the anthracenyl groups. In contrast, the *si* face is fully accessible and hence the enol ether **5** attacks from the front side affording intermediate **9** with *S* configuration. The final cyclization of **9** occurs preferentially by attack of the oxygen of the carbonyl group from the *re*-face of the oxonium group to deliver product **4**.

In summary, we have developed a new and straightforward synthetic protocol for the enantioselective synthesis of spiroacetals using a gold-phosphate catalysed one-pot three-component coupling reaction between alkynols, anilines and glyoxylic acid in a process where the only by-product is water. This reaction represents one of the very few examples of reagent-controlled asymmetric synthesis of spiroacetals and the first based on a multicomponent coupling process. The products obtained could be considered as hybrid molecules comprising a spiroacetal unit (a natural-product inspired scaffold) and an α-amino acid motif (a privileged fragment).

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