Acetonides as Masked Nucleophiles in the Gold-Catalyzed Spiroketalization of Monopropargylic Triols.

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Keywords: Gold-Catalysis, Spiroketal/Spiroacetal, Monopropargylic Triols

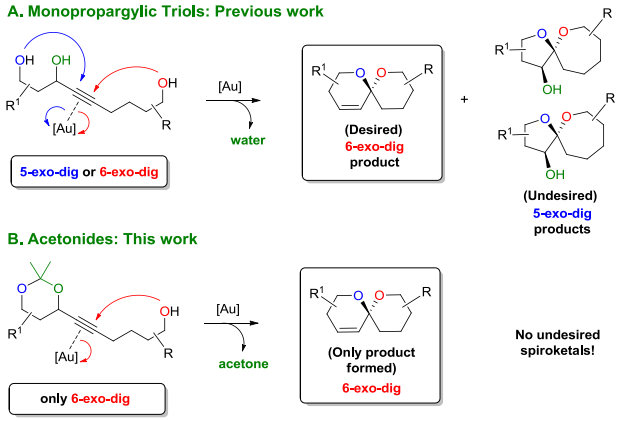
INTRODUCTION

Spiroketal-containing natural products are found in insects, plants, bacterial, and marine sources.[1] These natural products often display remarkable biological activity and their stereocontrolled synthesis remains a challenge.[1] Within this context, a gold-catalyzed synthesis of unsaturated spiroketals was accomplished by our group via dehydrative cyclization of monopropargylic triols.[2]

RESULTS AND DISCUSSION

This report shows a novel synthesis of unsaturated spiroketals and has already been applied in natural product synthesis,[3] however in some cases poor regioselectivities have been observed (Scheme 1A).

To overcome this issue, we hypothesized that acetonides derived from monopropargylic triols could be used instead, and this could force the 6-exo-dig cyclization to occur exclusively, generating only the desired unsaturated spiroketals, avoiding formation of the undesired ring-systems (Scheme 1B).

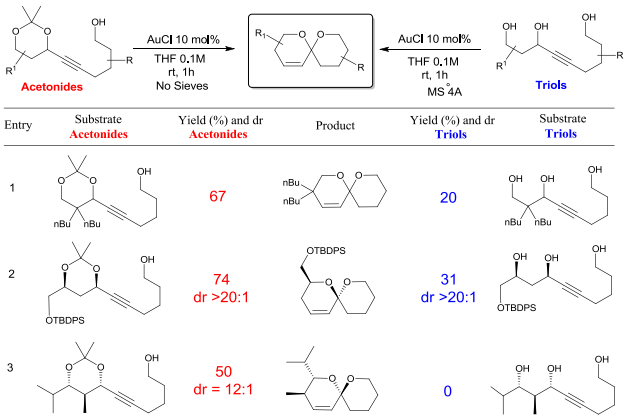


Scheme 1. Gold-catalysis in the synthesis of unsaturated spiroketals.

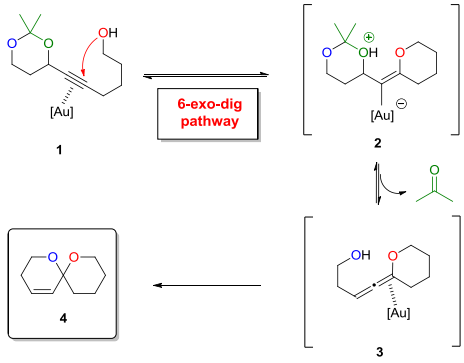
The use of AuCl in THF was deemed to be the optimal conditions for this cyclization. The reaction scope was then explored with different acetonides, and a comparison was made to the corresponding triols (Table 1).

Mechanistically, it is postulated that a gold-catalyzed 6-exo-dig cyclization takes place on the acetonide **1** to generate **2**, which undergoes synthesis of the allenylether **3** (Scheme 2). The success of the formation of **3** is expressly related to the fact that acetone was also a leaving group in this gold-catalyzed spiroketalization. Finally, cyclization of the intermediate **3** delivers the desired spiroketal **4**.

Table 1. Select substrate scope studies.



Experimental mechanistic studies corroborate that an allenylether such as **3** can be formed during the reaction, and evidence for its formation will be presented.



Scheme 2. Catalytic cycle for the spiroketalization of acetonides.

CONCLUSION

A novel gold-catalyzed synthesis of spiroketals from acetonides derived from monopropargylic triols is presented. This has targeted regioselectivity issues associated with the previously reported cyclization of triols. Importantly, mechanistic studies show that an allenylether can be formed throughout the course of the reaction.

ACKNOWLEDGEMENTS

We thank the University of Florida, the Herman Frasch Foundation (647- HF07), and the James and Ester King Biomedical Research Program (09KN-01) for their generous support of our programs.

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[3] Fang, C.; Pang,Y.; Forsyth, C. J. *Org. Lett.* **2010**, *12*, 4528-4531.