Multicomponent Reactions

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A Palladium(II)-Catalyzed Synthesis of Spiroacetals through a One-Pot Multicomponent Cascade Reaction**

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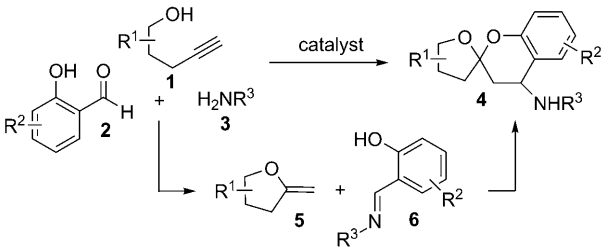
Spiroacetals are molecular frameworks found in many biologically active natural products such as insect pheromones, polyether ionophores, steroidal saponins, polyketide antibiotics, and metabolites derived from algae and fungi.[1] Interestingly, it has been shown that simplified spiroacetals derived from natural products retain their biological activity.[2] In this context, the design and synthesis of natural-product-like spiroacetal derivatives as potential orally bioavailable lead compounds has been reported.[3] By far, the most commonly used strategy in spiroacetal synthesis involves the cyclization of a dihydroxyketone.[4] This approach requires preforming the starting dihydroxyketone, generally this is done through a linear synthetic sequence. This preformation can be limiting in terms of the synthesizing spiroacetals with substituent variation, namely, in the preparation of compound libraries. A much more appealing strategy would involve the assembly of the spiroacetal framework through a one-pot multicomponent coupling reaction.[5] By following this protocol and by simple variations in the structure of some of the starting materials, it would be very easy to access small libraries of differently substituted spiroacetal derivatives.

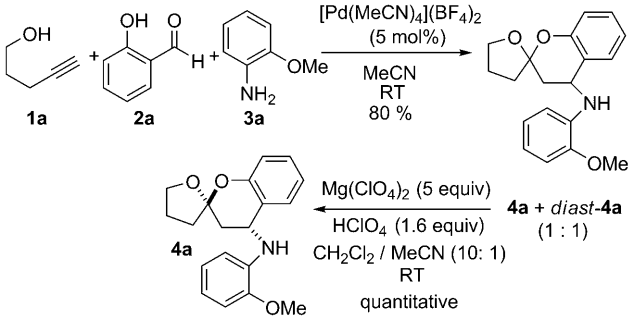
With this in mind, and following our interest in the development of new cascade catalytic reactions,[6] we considered the process shown in Scheme 1 as a potentially useful approach for the synthesis of chroman spiroacetals. Notably, the chroman spiroacetal skeleton is found in several recently discovered natural products such as berkelic acid[7] and paecilospirone.[8]



Scheme 1. Concept of the catalytic multicomponent coupling reaction for the synthesis of spiroacetal derivatives.

We hypothesized that an intramolecular hydroalkoxylation reaction of alkynols **1**, catalyzed by an appropriate metal complex, would provide exocyclic enol ethers **5**, which in the presence of imines **6** (formed in situ by condensation of salicylaldehyde derivatives **2** and amines **3**) would react to form spiroacetal derivatives **4** in an apparently very simple way from easily available starting materials (Scheme 1).

At the outset of this study, our efforts were directed at discovering the appropriate catalyst and reaction conditions to perform the proposed reaction. After some optimization studies, we found that the treatment 4-pentyn-1-ol **1a**, salicylaldehyde **2a**, and amine **3a** with 5 mol% of $[Pd(MeCN)_4](BF_4)_2$ in acetonitrile (as the solvent) at room temperature led to the formation of a 1:1 mixture of the spiroacetals **4a** and *diast*-**4a** in 80% yield (Scheme 2).



Scheme 2. Synthesis of spiroacetal **4a** through a catalytic three-component coupling reaction followed by equilibration.

Although this was an excellent result, a drawback was the formation of an equimolar mixture of diastereomers. To get a single diastereoisomer, we treated the crude mixture of **4a** and *diast*-**4a** with 5 equivalents of $Mg(ClO_4)_2$ and 1.6 equivalents of $HClO_4$ in dichloromethane/acetonitrile (10:1).[9] Under these reaction conditions we observed the clean and complete conversion of *diast*-**4a** into **4a** (Scheme 2).[10]

The scope of this new procedure was surveyed by probing changes to the alkynol **1**, the aldehyde **2**, and the amine **3**. As shown in Scheme 3, several spiroacetals were synthesized and isolated in high yield and as single diastereoisomers. The flexibility of the method allows the strategic placement of functionality at several positions. For example **4b**,**i**, with fluorine atoms in their structures, were easily prepared. Halogenated **4c**,**e**,**f**,**i** could be further functionalized through well established carbon–carbon coupling reactions. Structural

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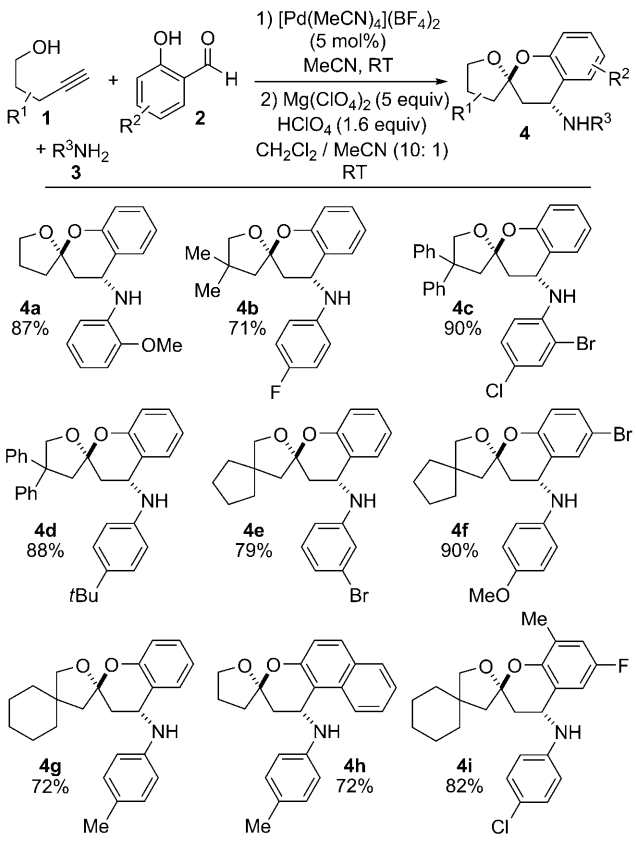
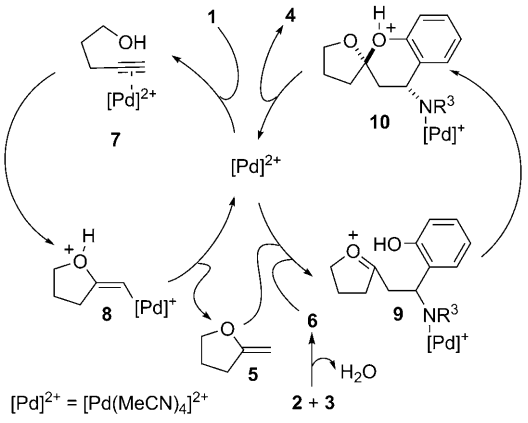


Scheme 3. Palladium(II)-catalyzed synthesis of spiroacetals **4** from alkynols **1**, aldehydes **2**, and amines **3**.

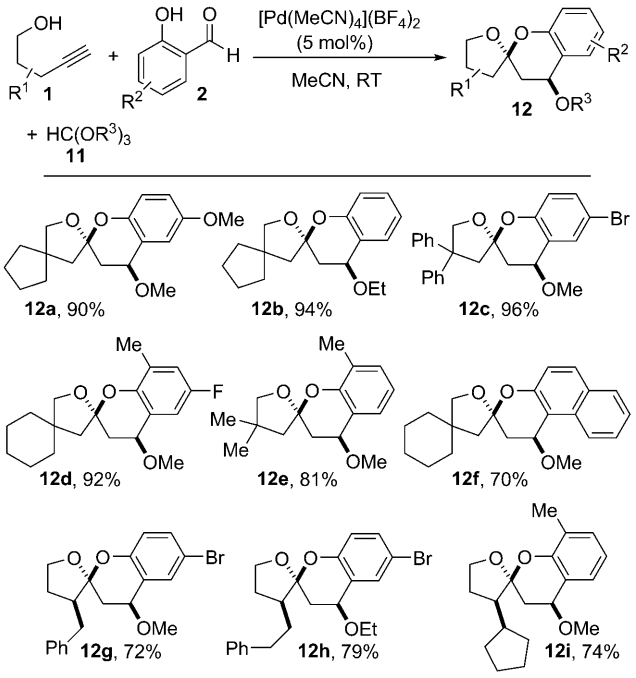
assignments of these new compounds were based on a series of NMR studies. Additionally, the structure of compound **4d** was confirmed by single crystal X-ray diffraction analysis.[11]

A plausible mechanism that explains these results has been proposed and is shown in Scheme 4. Thus, the reaction is initiated by coordination of the cationic palladium complex to the triple bond of the starting alkynol **1** to form intermediate **7**. Intramolecular addition of the hydroxy group to the internal carbon of the triple bond generates **8**. Protodemetalation of the latter affords the enol ether **5** and releases the catalytic species.[12] Once **5** is formed, it enters the second catalytic cycle where it reacts with the imine **6**, which is previously formed by condensation of aldehyde **2** and amine **3**. Thus, the coordination of the nitrogen atom of **6** to the palladium catalyst favors the addition of **5** to give the oxonium intermediate **9** through a Mannich-type process.[13] Intramolecular nucleophilic addition of the hydroxy group to the oxonium ion gives **10** that evolves through a protodemetalation reaction to furnish the final product **4**, and thereby closes the second catalytic cycle.



Scheme 4. A mechanism of the formation of spiroacetals **4**.

As shown, the reaction already described allows the synthesis of nitrogen-substituted chroman spiroacetals. With the aim to further develop the synthetic utility of the method, we then focused on the synthesis of oxygen-substituted chroman spiroacetals. To access these compounds it was evident that the third component of our reaction, the amine **3**, should be replaced by a reagent that would provide the oxygen function.[14] After some optimization studies, we found that the treatment of pentynol derivatives **1** with salicylaldehydes **2** and orthoesters **11** with 5 mol% of $[Pd(MeCN)_4](BF_4)_2$ in acetonitrile (as the solvent) at room temperature led to the formation of the desired spiroacetals **12** in high yield and as single diastereoisomers in all cases (Scheme 5). Surprisingly, the relative configuration of the carbon atom carrying the alkoxy group in **12** is the opposite of that observed in the nitrogen-substituted spiroacetals **4**. Also notable is the fact that in the synthesis of spiroacetals **12** the single diastereoisomers were directly obtained—it was unnecessary to perform the isomerization step that was required in the synthesis of spiroacetals **4**. The scope of the reaction was surveyed by probing changes to the alkynol, the aldehyde, and the orthoester substrates. Again, the flexibility of the method allows the strategic placement of functionality at several sites within the molecule. The spiroacetals **12g–i** are remarkable



Scheme 5. Palladium(II)-catalyzed synthesis of spiroacetals **12** from alkynols **1**, aldehydes **2**, and orthoesters **11**.

because they are derived from chiral alkynol derivatives **1**. In these cases, we only observed the formation of a single diastereoisomer corresponding to those structures shown in Scheme 5.[15] These results are significant as they indicate that the substrate-controlled synthesis of enantiomerically pure spiroacetal derivatives **12** is possible. Structural assignments of these new compounds were based on a series of NMR studies. Additionally, the structure of compound **12c** was confirmed by single crystal X-ray diffraction analysis.[11]

The formation of spiroacetals **12** is easily explained by a mechanism similar to that shown in Scheme 4. The only difference is the formation of an acetal intermediate, by reaction of the salicyladehyde and the orthoformate, instead of the imine **6**.[16]

In summary, we have developed a new and straightforward synthetic protocol for the diastereoselective construction of spiroacetals.[17] The reaction supposes a palladium(II)-catalyzed one-pot three-component coupling reaction between an alkynol derivative, an aldehyde, and an amine or an orthoester substrate. The easy generation of molecular diversity along with the importance of chroman spiroacetals in medicinal chemistry makes the reaction described here an appropriate alternative for the synthesis of potentially bioactive compounds. In this context, and considering the simplicity of the starting materials, the reaction seems suitable for the synthesis of small libraries of functionalized spiroacetals.

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[11] CCDC 707907 (**4d**), 707906 (**12c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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