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Synthesis of Spiroquinolines through a One-Pot Multicatalytic and Multicomponent Cascade Reaction**

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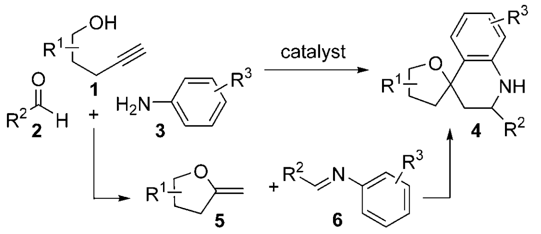
Dedicated to Professor Josep Font on the occasion of his 70th birthday

The role played by organic chemistry in the pharmaceutical industry continues to be one of the main drives in the drug discovery process. More than ever, the industry demands from organic chemists the development of new strategies and technologies to obtain novel compounds in a fast, clean, and efficient way. Among these procedures are multicomponent reactions (MCRs) which offer the opportunity of building up complex molecules with exceptional synthetic efficiency, frequently with high stereoselectivity, from simple and easily available substrates.[1] Among MCRs, the Povarov reaction (the reaction of an aromatic imine and an activated olefin) provides a powerful method giving access to quinoline derivatives.[2] As a consequence of their relevant pharmacological profile,[3] the search for new methodologies to synthesize this kind of compounds is a research field of undoubted current attention.

Following our interest in the development of new catalytic cascade reactions,[4] we considered the possibility of synthesizing functionalized quinolines in a single synthetic operation from alkynol, aldehyde, and aniline substrates (Scheme 1). Thus, we hypothesized that an intramolecular hydroalkoxylation reaction of alkynols **1**, which is catalyzed by an appropriate metal complex, would provide exocyclic enol ethers **5**. Subsequently, **5** and aromatic imines **6**, which are formed in situ by condensation of aldehydes **2** and anilines **3**, would react to form spirofuranquinoline derivatives **4** in a very simple way. Interestingly, this proposed reaction would circumvent one of the main limitations of the Povarov reaction—it is difficult to access functionalized starting enol ether reagents.[5] As far as we know, the Povarov reaction performed with exocyclic enol ethers has never been reported.



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

Our initial efforts were directed at finding the appropriate catalyst and reaction conditions to perform the proposed sequence. Regarding the catalyst for the intramolecular hydroalkoxylation of alkynols **1**, we considered platinum or gold complexes because of their ability to activate the alkyne functionality under mild conditions.[6] We also hypothesized that the required in situ formation of imines **6**, from aldehydes **2** and amines **3**, would be favored by the presence of a Brønsted acid. At the same time, this acid could also facilitate the addition of enol ether **5** to the imine **6** by coordination of the proton to the nitrogen atom of the imine. The cooperative action of both catalysts—the platinum complex and the Brønsted acid—in one pot would provide a new example of concurrent tandem catalysis.[7]

Taking into consideration all the above-mentioned points we thought that the combination of [$PtMe_2$(cod)] (cod = 1,5-cyclooctadiene) and HBF_4 would be ideal.[8] On the one hand, under the protic conditions the [$PtMe_2$(cod)] complex would be transformed into a highly reactive cationic platinum complex. On the other hand, the presence of the Brønsted acid would favor the formation of the imine and its subsequent reaction with the enol ether as previously discussed.

Thus, we initiated our studies with the reactions of several pentynol derivatives **1** with aldehydes **2** and anilines **3** in the presence of 5 mol% of [$PtMe_2$(cod)] and one equivalent of HBF_4 in acetonitrile, with temperatures ranging from −30 °C to room temperature. As shown in Scheme 2, these reactions led to the formation of the spiro[furan-2,4′-quinoline] derivatives **4** in high yield. The scope of the reaction was surveyed by probing changes to the alkynol, the aldehyde, and the amine substrates. The flexibility of the method allows the strategic placement of functionalities at several positions. For example **4c** and **4d**, which contain fluorine atoms in their structures, were easily prepared. Chlorinated compounds **4a**, **4h**, and **4l** could be further functionalized through well-established carbon–carbon coupling reactions. Of particular interest is spirofuranquinoline **4i** as it is highly functionalized and is obtained as a single diastereoisomer. In this example, a chiral alkynol derivative **1** was used and the stereocenter of

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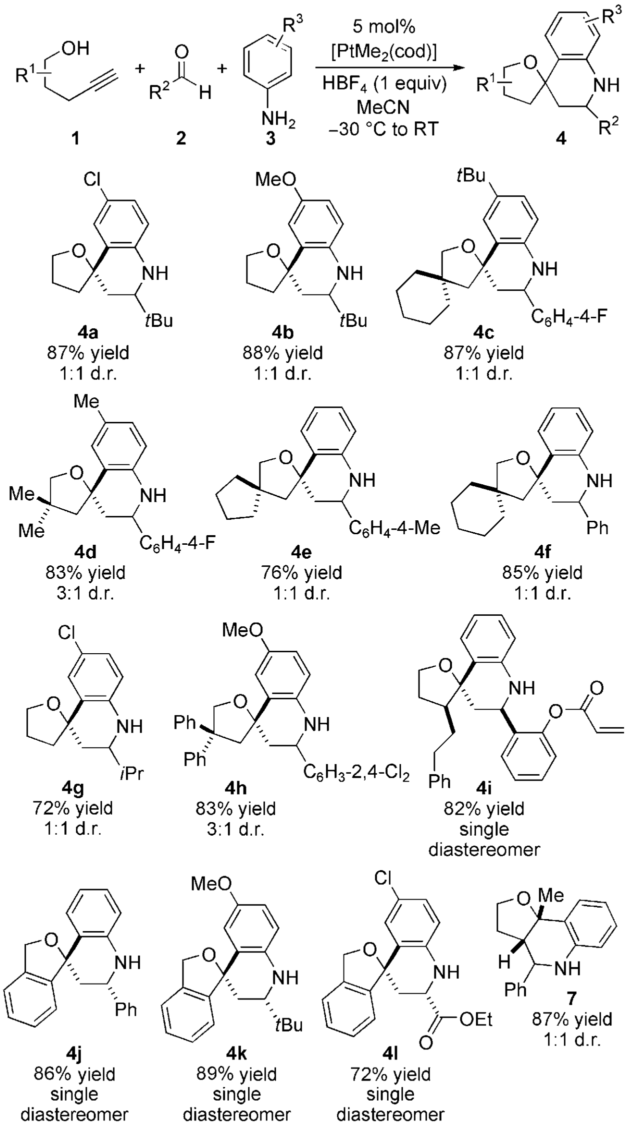


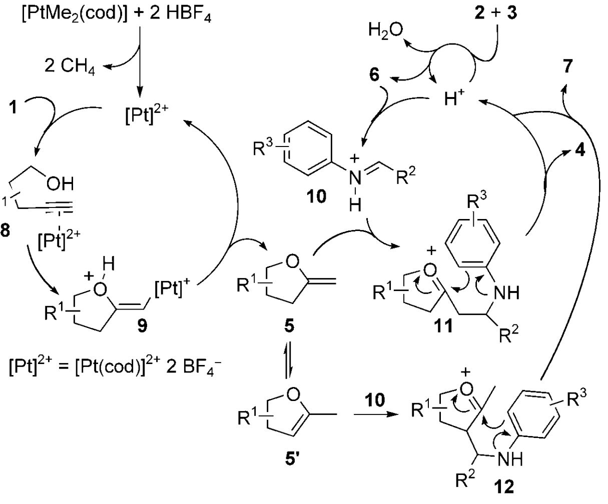
Scheme 2. Synthesis of spirofuranquinolines **4** and furoquinoline **7** through a catalytic three-component coupling reaction.

this starting material controls the chirality of the newly formed stereocenters. This result opens the door for the substrate-controlled synthesis of enantiomerically pure spiroquinoline derivatives **4**. Also remarkable is the product **4l**, which is also obtained as a single diastereoisomer, as it could be considered as an α-amino acid derivative. Interestingly, an appropriate substitution on the initial alkynol **1** would deliver products analogous to **4l**, whose structure is not far from that of the biologically relevant glycopeptide derivatives. Structural assignments of these new compounds were based on a series of NMR studies (see the Supporting Information). Additionally, the structures of **4c**, **4d**, and **4k** were confirmed by single-crystal X-ray diffraction analysis.[9]

The only unmatched result was found in the reaction of pentyn-1-ol, benzaldehyde, and aniline. In this case, we obtained the furo[3,2-*c*]quinoline **7** in high yield instead of the expected spirofuranquinoline analogous to **4** (see the last example in Scheme 2). This particular behavior seems to be limited to those cases where unsubstituted alkynol derivatives and aromatic aldehydes are used.[10]

Notably, similar results to those described in Scheme 2 were obtained by performing the reaction with the preformed imine **6**, which was synthesized in a separated vessel by condensation of aldehydes **2** and amines **3**.

A mechanistic proposal that explains these results is shown in Scheme 3. We suppose the formation of a reactive cationic platinum complex from [$PtMe_2$(cod)] by reaction with HBF_4 in a process where two molecules of methane are released.[11] Thus, the reaction is initiated by coordination of the metal complex to the triple bond of the starting alkynol **1** to form intermediate **8**. Intramolecular addition of the hydroxy group to the internal carbon atom of the triple bond generates **9**. Protodemetalation of **9** affords the enol ether **5** and releases the catalytic species. Once **5** is formed, it enters the second catalytic cycle where the protic acid is supposed to be the real catalytic species. Thus, the Brønsted acid catalyzes the formation of the imine **6** and a molecule of water is expelled from the reaction of aldehyde **2** and amine **3**. Further reaction of **6** with a proton renders the iminium salt **10**, which reacts with the preformed enol ether **5** to give the oxonium intermediate **11** through a Mannich-type process. Intramolecular nucleophilic addition of the electron-rich aromatic ring followed by a rearomatization step leads to the final products **4** and closes the second catalytic cycle as a proton is delivered in the rearomatization reaction.[12]



Scheme 3. Proposed mechanism for the formation of **4** and **7**.

To explain the formation of the furoquinoline **7**, an isomerization of the exocyclic enol ether **5** to the endocyclic **5′** prior to the addition to the iminium salt **10** is proposed. This isomerization is known to proceed under acidic conditions.[13] The reaction of **5′** and **10** furnishes the oxonium intermediate **12**, which evolves through intramolecular nucleophilic addition followed by a rearomatization step to give the product **7** and a proton that continues the catalytic cycle. Both the rate of isomerization of **5**→**5′** and the reactivity of the imine **6** (or the protonated species **10**) seem to be responsible for the formation of spiroquinolines **4** or the furoquinoline **7**. Thus, for imines derived from alkylic aldehydes the reaction always gives the spirofuranquinolines **4** independent of the alkynol **1** used, thus indicating that the isomerization of **5**→**5′** is slower than the addition of **5** to **10** to give **11** and finally compound **4**. However, when aromatic aldehydes are used, formation of **4** or **7** depends on the structure of the alkynol **1**. Thus, when 4-pentyn-1-ol is used the isomerization of **5**→**5′** seems to be faster than the addition of **5** to **10**. So, in these particular cases the reaction occurs between **5′** and **10** to give **12** and finally the furoquinoline **7**.

Moreover, both catalysts, the metal complex, and the Brønsted acid all seem to be necessary to achieve a positive outcome. Thus, in the absence of the platinum catalyst, formation of **4** does not occur to any extent and starting materials are recovered. On the other hand, under non-protic acid conditions the imine **6** is not formed and so the reaction does not take place.[14] Although a metal-catalyzed process could be proposed for the second catalytic cycle (the reaction of enol ether **5** and imine **6**)[15] we believed that a Brønsted acid catalyzed reaction is much more likely.[16]

In summary, we have developed a new and simple synthetic protocol for the construction of spirocyclic quinoline derivatives which are not easily available through traditional organic reactions. The approach supposes a one-pot three-component coupling reaction between an alkynol derivative, an aldehyde, and an aromatic amine. The process could be formally considered as the first Povarov reaction performed with exocyclic enol ethers. Interestingly, both reagents required for the Povarov reaction, the enol ether and the *N*-arylaldimine, are catalytically formed in situ from an alkynol, and from an aldehyde and an aniline, respectively. Also remarkable is the cooperative effect of two catalysts—a platinum complex and a Brønsted acid. In the context of searching for new pharmacological active compounds, the new reaction described here seems appropriate for the synthesis of small libraries of functionalized spirocyclic quinoline derivatives arising from the easy generation of molecular diversity.

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Keywords: cyclization · homogeneous catalysis · multicomponent reactions · platinum · quinolines

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[9] CCDC 689852 (**4d**), 689853 (**4k**), 689854 (**4c**) 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.

[10] Preliminary investigations seem to indicate that furoquinolines analogous to **7** are obtained only in those cases where the unsubstituted alkynol, 4-pentyn-1-ol, is used in the presence of aromatic aldehydes, and is independent of the aniline used. Details on this particular reaction will be given separately.

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