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# Formation of cinnoline derivatives by a gold(I)-catalyzed hydroarylation of *N*-propargyl-*N*′-arylhydrazines

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ABSTRACT

A study concerning the gold(I)-catalyzed hydroarylation of *N*-propargyl-*N*′-arylhydrazinecarboxylic acid methyl esters is described. The use of the gold complex [XPhosAu(NCCH$_3$)SbF$_6$] as the catalyst in refluxing nitromethane allows the generally rapid and efficient synthesis of a range of functionalized 4-*exo*-methylene-1,2-dihydrocinnolines.

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## 1. Introduction

While being less frequently used than the quinoline heterocycle, the isosteric cinnoline moiety remains a structural unit of choice in medicinal chemistry for the discovery of new biologically active substances (Fig. 1) [1]. The continuous attention which has been paid over the past 50 years to the development of new strategies allowing the efficient synthesis of heterocyclic compounds possessing a cinnoline moiety is mainly due to the exceptional spectrum of pharmaceutical activities exerted by such molecules [1]. The use of cinnoline derivatives in drug design has also been investigated and several tetrahydrocinnolines [2] and 1,2-dihydrocinnolines [3], such as compound **1** or the marketed drugs cinnopentazone **2** and cinnofuradione **3**, have been reported as bioactive molecules.

Given the general interest in the cinnoline motif and following our continuous interest in the field of gold-catalyzed synthesis of nitrogen containing heterocycles [4], we envisaged developing a new access to molecules possessing either a tetrahydro- or a dihydrocinnoline unit in their structure. Our synthetic approach is depicted in Scheme 1. It is based on our recent finding that a wide range of *N*-aminophenyl propargyl malonates **4** can be easily converted into tetrahydroquinolines **5** following a gold(I)-catalyzed hydroarylation process [5,6]. By analogy with this transformation, we surmised that the *N*-propargyl-*N*′-arylhydrazine derivatives **6** might be transformed into the corresponding tetrahydrocinnolines **7** by a nucleophilic addition of the aromatic nucleus onto the gold(I)-activated alkyne [7]. The hydroarylation product **7** would be subsequently converted into 1,2-dihydrocinnolines **8** by treatment with an acid.

It is important to note that the gold(I) formation of tetrahydroquinolines **5** we recently reported could only be performed with substrates **4** possessing a basic nitrogen atom (i.e. $R^2$ = alkyl or aryl) [8]. Moreover, the efficiency of this transformation was directly associated with the presence of the malonate moiety that was supposed to prevent or limit the coordination of the gold(I) complex with the nitrogen atom probably through steric and electronic effects [9]. These results caused us to initially question the possibility of performing an analogous gold(I)-catalyzed hydroarylation on hydrazine derivatives **6** as it was supposed in this case that the nitrogen atom attached to the aromatic nucleus would be more accessible and therefore more prone to coordination than that in substrates **4**. We report herein our investigations in this domain which have led to the development of a new synthetic approach to functionalized cinnoline derivatives.

## 2. Results and discussion

*N*-Propargyl-*N*′-phenylhydrazine derivative **9**, easily and efficiently obtained in a two steps sequence from diethyl azadicarboxylate (DEAD), was first chosen as a model substrate to validate our synthetic approach to tetrahydrocinnolines (Scheme 2).

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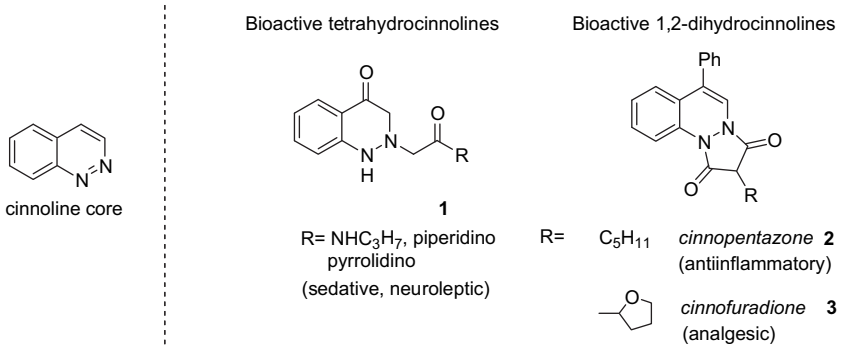
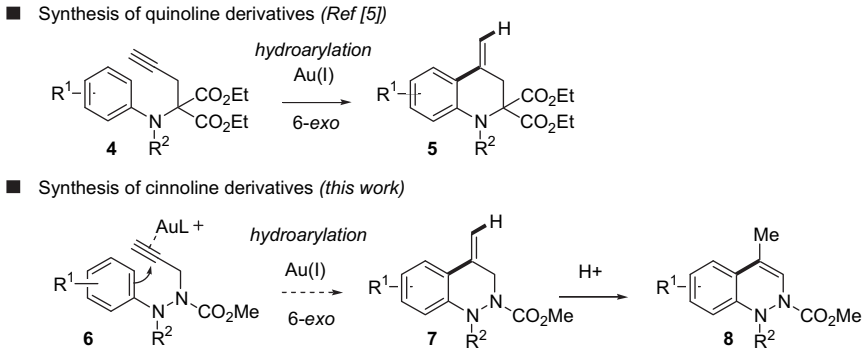


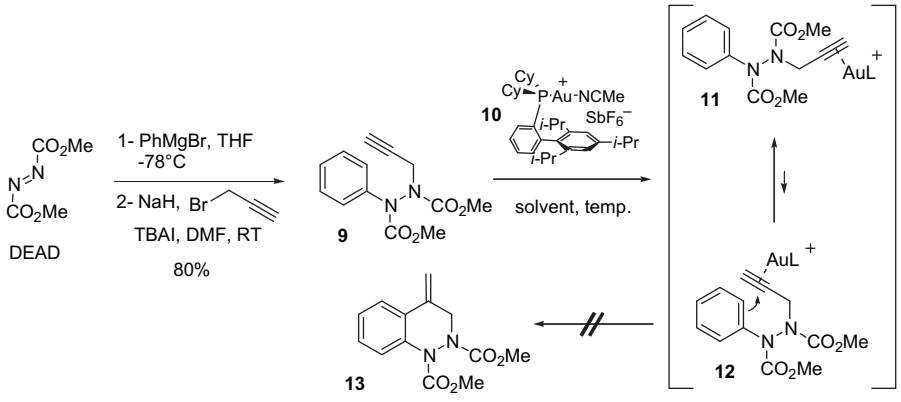

**Fig. 1.** Example of bioactive 1,2-dihydro- and tetrahydrocinnolines.




**Scheme 1.** Synthetic approach to cinnoline derivatives.

However, under the optimal catalytic conditions previously used for the hydroarylation of *N*-aminophenyl propargyl malonates **4** (1 mol% of gold complex [XPhosAu(NCCH$_3$)SbF$_6$] **10** in refluxing nitromethane) [5], no formation of the *exo*-methylene tetrahydrocinnoline **13** could be observed. Using a higher catalyst loading or changing the nature of the solvent and the reaction temperature was not beneficial. Such a negative result might be attributed to the presence of two possible conformers **11** and **12** among which the cyclizing one (**12**) should be less favoured due to a steric interaction and/or a dipole repulsion between the two carboxymethyl moieties. The reduced nucleophilicity of the phenyl nucleus, due to the presence of the carboxymethyl group on the nitrogen atom attached to the aromatic, might also be invoked to explain the inertness of **9** [5]. To circumvent this problem and in order to increase the nucleophilicity of the aryl group, one of the carbamate moiety was therefore replaced by another phenyl group (Scheme 3).

The treatment of compound **14** with 1 mol% of gold complex **10** in refluxing nitromethane did not allow the formation of the desired cinnoline derivative **15**. However, the use of a higher




| 10 | SolventT | emp. | Time | Yield 13 |
|---|---|---|---|---|
| 1 mol% | $CH_3NO_2$ | 100℃ | 3h | 0% |
| 4 mol% | $CH_3NO_2$ | 100℃ | 24h | 0% |
| 4 mol% | toluene | 110℃ | 24h | 0% |

**Scheme 2.** Hydroarylation attempt with arylhydrazine **9**.

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