Journal of Fluorine Chemistry 171 (2015) 60–66

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

# Differential reactivity of fluorinated homopropargylic amino esters vs gold(I) salts. The role of the nitrogen protecting group

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ARTICLE INFO

*Article history:*
Received 10 July 2014
Received in revised form 15 September 2014
Accepted 17 September 2014
Available online 6 October 2014

*Keywords:*
Fluorinated homopropargyl amino esters
Gold catalysis
Fluorinated dihydro-quinolines
Fluorinated oxazines
Fluorinated alfa-amino acid derivatives

ABSTRACT

The reaction of several homopropargyl amino esters **4**, bearing aromatic substituents and a benzyl group as nitrogen substituents, with gold(I) salts gave rise to fluorinated quinolines **6** in a tandem hydroarylation–isomerization process. On the other hand, homopropargyl amino esters **7** containing a carbamate group underwent the carbonyl addition over the triple bond in the presence of gold(I) salts, rendering fluorinated oxazines **8**. The use of chiral sulfoxides allowed us to develop the asymmetric version of this protocol. This two processes complete the differential reactivity showed by these types of susbtrates, depending on the nature of the nitrogen protecting group.



## 1. Introduction

Homogeneous gold catalysis has witnessed an extraordinary growth in the last decade, becoming among the most efficient methodologies for the creation of carbon–carbon or carbon–heteroatom bonds [1].

Homopropargylic amines are ubiquitous substrates in gold catalysed reactions [2]. Taking advantage of the ability of gold salts to activate alkynes vs the addition of several nucleophiles under mild conditions, those compounds have been used as suitable starting materials in processes that involve an initial intramolecular hydroamination of the triple bond. The subsequent combination of this carbon–nitrogen bond formation with further transformations in a tandem or a *one pot* manner was traduced in the development of new methodologies for the preparation of several nitrogen containing heterocycles. However, very few reports concerning the use of fluorinated starting materials have been devised to date. This is probably due to the absence of efficient methods to access fluorinated propargylic amines.

In this context, fluorinated homopropargylic amino esters were synthesized to date by addition of allenyl magnesium bromide to the corresponding imino esters [3]. However, only highly electrophilic imino esters (bearing carbamates or sulphonamides at the nitrogen end) were compatible with this methodology. Resulting amino esters have been used as starting materials in dipolar type cycloadditions with azides or nitrile oxides [1,4]. Sonogashira-type coupling reactions were employed to functionalize these compounds at the terminal alkyne [5]. Alternatively, the propargylation of the nitrogen afforded the corresponding *N*-alkylated derivative that reacted with another alkyne in the presence of a ruthenium catalyst to render the cyclotrimerization product [6]. Finally, very recently, those substrates were subjected to an acid-catalyzed intramolecular hydroamination reaction that afforded, after imine-reduction, the corresponding pyrrolidines [7]. However, the reactivity of those alkynes with gold salts was never tested to date.

## 2. Results and discussion

In an ongoing project in our laboratory, we decide to explore this type of reactivity. We envisioned the possibility of performing a differential reactivity of those amino esters in the presence of gold salts, just by changing the substitution pattern of the nitrogen. Hence, we could expect that with substrates containing an

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http://dx.doi.org/10.1016/j.jfluchem.2014.09.017
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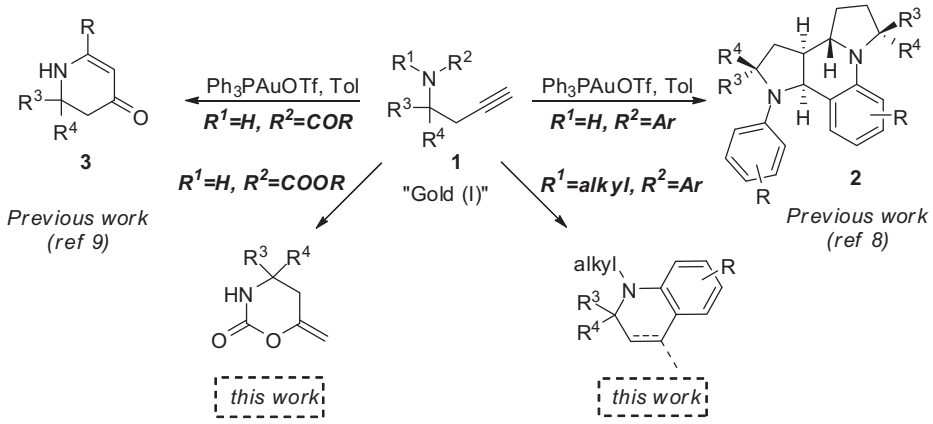



**Scheme 1.** Differential reactivity of quaternary homopropargyl amines **1** under Au(I) catalysis.

aromatic substituent ($R^1$ = H, $R^2$ = Ar) a hydroamination type of process would occur. Indeed, these starting materials evolved in the presence of $Ph_3PAuOTf$ in toluene at rt in a tandem protocol that started with the nitrogen addition to the activated triple bond by the gold salt. Once that this product is formed, an intermolecular aza-Diels Alder took place rendering tetracycles **2** with high levels of diastereoselectivity (Scheme 1) [8]. On the other hand, when this nitrogen was protected as an amide group ($R^1$ = H, $R^2$ = COR) the carbonyl addition over the triple bond could be expected. Again, after the initial addition, the intermediate oxazine underwent a tandem protocol affording a new family of 2,3-dihydropyridin-2.3(1*H*)-ones **3** (Scheme 1) [9]. We envisioned that in substrates containing an aromatic substituent, the blockage of the NH bond ($R^1$ = alkyl, $R^2$ = Ar) by alkylation would avoid the hydroamination step, and a hydroarylation-type process could be expected instead, giving rise to quinoline derivatives (Scheme 1) [10]. Finally, in homopropargyl amines bearing carbamates, a carbonyl addition over the triple bond activated by the gold(I) salt could be expected, affording in this case the corresponding oxazines (Scheme 1) [11]. Herein we report the evaluation of these two types of reactivity patterns, which would complete the differential reactivity showed by these homopropargylic amino esters.

Initially, we evaluated the hydroarylation type of reactivity [12]. To this end, it was necessary to block the NH of substrates **1** bearing an aromatic substituent by alkylation. The introduction of alkyl groups in compounds **1** proved to be troublesome. This is probably due to the low nucleophilicity of the nitrogen, since the alfa-carbon contains two electron-withdrawing groups. After several attempts, only substrates containing a PMP group (4-MeO-$C_6H_4$) were alkylated (probably because this group increase the basicity of the nitrogen) and the conditions involved the treatment of substrates **1** with benzyl bromide, using $NaHCO_3$ as base with a catalytic amount of KI in $CH_3CN$, heating the reaction mixture in a sealed tube at 100 °C for 5 days. In this manner, moderate yields of benzylated propargylic amines **6** were isolated in moderate yields (Scheme 2).

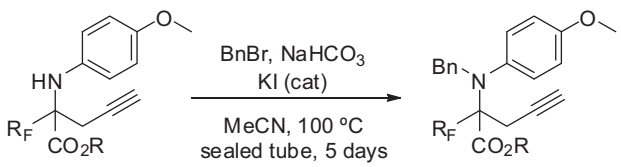
With substrates **4** in hand, compound **4a** was used as a model substrate to evaluate its reactivity vs gold salts. Initially, we tested AuCl and $AuCl_3$ as a gold source in the process, but **4a** was inert in those conditions, probably due to solubility problems (Table 1, entries 1, 2). The change to $PPh_3AuCl$ as gold salt was crucial, and an equimolecular mixture of **5a** and **6a** was detected in 69% yield (Table 1, entry 3). While **5a** is the regular hydroarylation product, **6a** arise from a tandem hydroarylation–isomerization process. The use of other solvents and temperatures was traduced in an improvement of the **5a:6a** ratio but in detriment of the final yield (Table 1, entries 4–6). Other silver salts again product a better **5a:6a** ratio but led to the final products in only moderate yields (Table 1, entries 7–9). Finally, the influence of the gold salt was evaluated. With gold salts bearing phosphines with electron withdrawing groups (catalyst **II**), NHC ligands (catalyst **III**) or gold salt **IV** comparable results were obtained (Table 1, entries 10–12). Finally, we found that gold salt **V** with a phosphite ligand gave the best result in terms of yield and **5a:6a** ratio (Table 1, entry 13). The silver salt itself or triflic acid did not catalyze the process (Table 1, entries 14–15).

The optimum conditions were further extended to the rest of substrates **4**, giving rise to a new family of fluorinated quinoline derivatives **6** (Scheme 3).

To complete the differential reactivity of homopropargyl amino esters **1** vs gold salts, we synthesized the corresponding starting materials bearing a carbamate as nitrogen protecting group. Using compound **7a** as model substrate, we tested its reactivity vs gold salts. First attempts were made with AuCl and $AuCl_3$ and in this case, moderate yields of the oxazine **8a**, derived from the carbonyl addition over the triple bond, were obtained (Table 2, entries 1, 2). A significant improvement was observed with $PPh_3AuCl$, giving rise to **8a** in 71% yield in only 30 min (Table 2, entry 3). The yield increased until 91% when the reaction was performed in toluene (Table 2, entry 4). The use of other gold salts (Table 2, entries 5, 6) or other silver salts in the process (Table 2, entries 7–9) did not improve the efficiency of the reaction.

The optimum conditions were further extended to the rest of substrates **7**, giving rise to a small family of fluorinated oxazine derivatives **8** (Scheme 4) [13].

Finally, the asymmetric version of this protocol was evaluated. To this end, trifluoropyruvate **9** was treated with chiral phosphazene **10** to render the corresponding imino ester that was




**1a** ($R_F$=$CF_3$, R=Et)
**1b** ($R_F$=$CF_2Cl$, R=Et)
**1c** ($R_F$=$CF_2Ph$, R=Et)
**1d** ($R_F$=$CF_2Allyl$, R=Bn)

**4a** (92%, 58% conv)
**4b** (48%, 39% conv)
**4c** (72%, 64% conv)
**4d** (37%, 53% conv)

**Scheme 2.** Preparation of benzylated homopropargyl amino esters **4**.