

Gold catalyzed synthesis of fluorinated tetrahydrofurans and lactones



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ABSTRACT

The gold catalyzed tandem cycloisomerization/fluorination of alkynylic alcohols gives difluoro hydroxyl tetrahydrofurans at room temperature in moderate to good yields. The gold catalyzed monofluoro-lactonization of alkynylic acids to the corresponding fluoro lactones was also explored.

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1. Introduction

Fluorine substitution is a proven successful strategy in pharmaceutical, agrochemical and materials research [1–4]. And, gold catalysis is regarded as one of the most important additions to the field of organic synthesis in the past decade [5–12]. But successful gold catalyzed fluorinations are still limited, compared to other transition metals like Pd and Cu [13]. The first gold-catalyzed nucleophilic hydrofluorination of alkynes to form fluoroalkene was developed by the Sadighi's group using $\text{Et}_3\text{N}\cdot 3\text{HF}$ as a nucleophilic fluorination reagent [14,15]. Gouverneur's group developed the first gold-catalyzed fluorination of alkyne using an electrophilic fluorination reagent (Selectfluor) [16]. Our group developed a gold catalyzed multi-component transformation – functionalized hydration of alkynes, where various functionalized fluoroketones can be accessed in one pot [17]. Both Nevado (Scheme 1a) [18] and Gouverneur groups (Scheme 1b) [19] have independently developed an efficient gold-catalyzed rearrangement and fluorination of propargyl acetates **1**. Later, Nevado and coworkers developed a synthesis of α -fluoroketone or α -fluoroacetal **6** using similar conditions (Scheme 1c) [20]. Liu and Xu reported the synthesis of fluorinated pyrazoles via a gold catalyzed tandem aminofluorination of alkyne **7** in the presence of $\text{Ph}_3\text{PAuNTf}_2$, Selectfluor and base (NaHCO_3) (Scheme 1d) [21]. This reaction also produced significant amounts of nonfluorinated pyrazole [21]. Fensterbank and coworkers reported the formation of fluoromethylene pyrrolidines **10** using a combination of gold

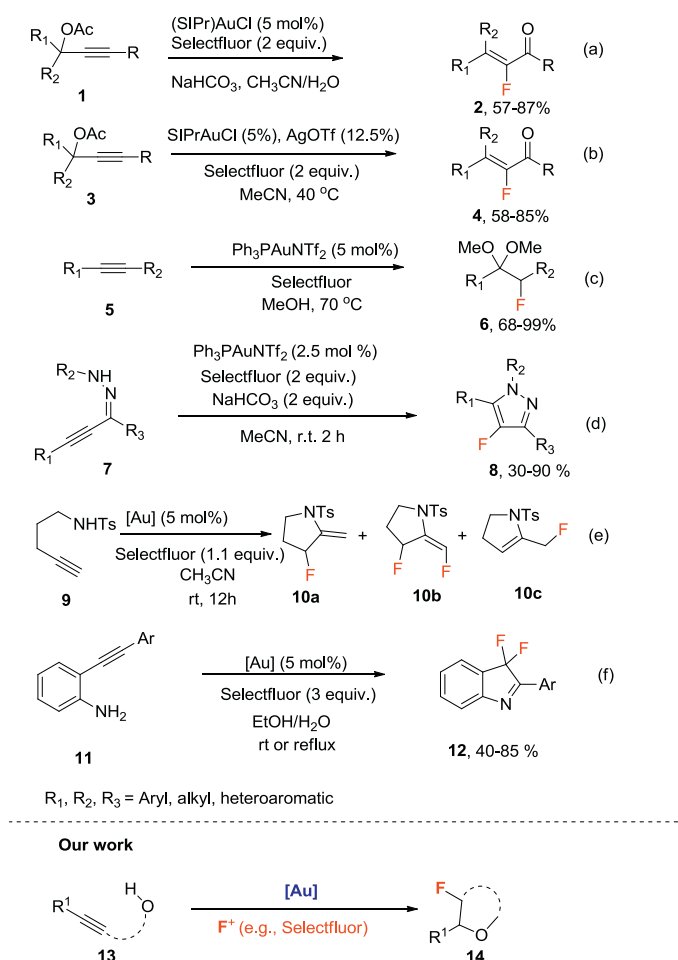
catalyst and Selectfluor (Scheme 1e) [22]. Most recently, Michelet and coworkers developed a gold catalyzed tandem aminofluorination for the synthesis of difluorinated indoles **12** from 2-alkynylanilines **11** using Selectfluor as well (Scheme 1f) [23].

Our focus is the synthesis of fluorinated oxygen heterocycles through a gold/electrophilic fluorination reagent combination (Scheme 1, bottom). To the best of our knowledge, these fluorinated oxygen heterocycles, like tetrahydrofurans, are relatively unknown and could serve as potential building blocks in synthesis.

We selected alkynylic alcohol **13a** as our model substrate because it is readily prepared by the reduction of corresponding β -alkynyl ester [24]. Various gold catalysts were screened using Selectfluor (F-TEDA-BF_4) as fluorinating agent (Table 1). We were pleased to observe that **13a** underwent fluorocyclization in the presence of PPh_3AuCl and Selectfluor to furnish the fluorinated hydroxyl tetrahydrofuran substrate **14a** in 52% yield in 3 h at room temperature (Table 1, entry 1). Other gold catalysts such as AuCl_3 , $\text{PPh}_3\text{PAuNTf}_2$, IPrAuCl , $(p\text{-CF}_3\text{Ph})_3\text{PAuCl}$ and **Au-1** (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate) were also screened and the best result was obtained using $(p\text{-CF}_3\text{Ph})_3\text{PAuCl}$ (Table 1, entry 5) as a catalyst. Increasing the amount of Selectfluor to 4 equiv did not improve the yield (Table 1, entry 7). Also, longer reaction times (24 h) had no influence on the yield of the reaction (Table 1, entry 8). Using a stronger base such as potassium carbonate proved detrimental to the reaction and no desired fluorinated product was obtained (Table 1, entry 9). Other bases such as dipotassium phosphate (K_2HPO_4) and sodium acetate (NaOAc) were not helpful (Table 1, entries 15 and 16). Adding nucleophilic fluoride sources such as KF, CsF and tetramethylammonium fluoride (TMAF) gave sluggish reactions and lower yields (Table 1, entries 14, 17 and 18).

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Scheme 1. Previous reports on gold catalyzed fluorination of alkynes and our work.

With the optimized reaction condition (Table 1, entry 5) in hand, we explored the scope for the synthesis of difluorotetrahydrofurans **14** (Table 2). We found that for some substrates the yield was relatively low using Selectfluor as the fluorinating agent (Table 2, compound **14b**). Replacing Selectfluor (F-TEDA-BF₄) with F-TEDA-PF₆ as the electrophilic fluorinating agent gave a much better yield (94%) (Table 2, compound **14b**). This significant

increase in the yield could be accounted by the more electrophilic nature of F-TEDA-PF₆ with respect to Selectfluor [25]. So, we used F-TEDA-PF₆ as the electrophilic fluorinating reagent for most of the substrates in Table 2. A substrate with an electron-rich aromatic ring (**13c**) gave **14c** in moderate yield. An alkene functional group was well tolerated (Table 2, **14d**, 84% yield); however, the isopropyl substituted alkynylic alcohol **13e** furnished a relatively lower yield of **14e**. A second hydroxyl group was well tolerated (Table 2, **14f–14g**). Highly sterically hindered substrates gave lower yields of **14** (Table 2, **14i**).

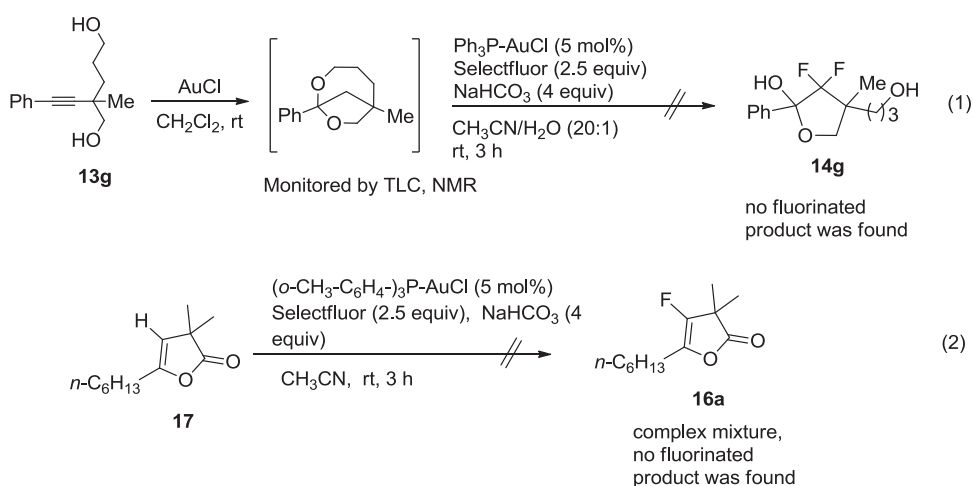
We tried to synthesize other fluorinated oxygen heterocycles using a similar protocol. The gold catalyzed electrophilic monofluorolactonization of alkynylic acid **15** [24] produced monofluoro lactone **16** at room temperature (Table 3). Different gold catalysts such as (*o*-CH₃Ph)₃AuCl, JohnPhos-Au-Cl and dichloro(2-pyridinecarboxylato)gold were screened but all of them produced a mixture of fluoro furanones along with the formation of protonated byproduct **17**. We observed that when 3 Å molecular sieves were introduced into the reaction, 68% of the desired mono fluoro product **16** was observed (Table 3, entry 3).

We also investigated the plausible mechanism for the formation of **14** and **16** (Scheme 2). A standard gold catalyst can cyclize **13** and **15** to give non-fluorinated products in high yields (Scheme 2), but these non-fluorinated cyclized products failed to give any **14** or **16** under similar conditions as those used in Tables 1 and 3. These results indicated to us that the mechanism is not a simple two-step gold catalyzed cyclization/electrophilic fluorination sequence, but that a more complex mechanism might be operating in the reaction.

In summary, we have developed a gold catalyzed hydroxy-fluorination of alkynylic alcohols **13** using F-TEDA-PF₆ as fluorinating agent to form novel difluoro hydroxyl tetrahydrofuran substrates **14**. Various aromatic and aliphatic substituted alkynylic alcohols **13** were successfully converted to **14** in moderate to good yields. Also, the monofluorolactonization of alkynylic acids **15** was investigated and found to yield the corresponding fluoro-lactones **16**.

2. Experimental

General procedure for the synthesis of difluoro hydroxyl tetrahydrofurans (14): To a vial charged with F-TEDA-PF₆ (202.5 mg, 0.43 mmol), NaHCO₃ (57.8 mg, 0.68 mmol) was added, followed by the addition of CH₃CN:H₂O (1 mL, 20:1). The resulting mixture was stirred for 5–10 min. Then, **13b** (30 mg, 0.17 mmol) was added,



Scheme 2. Investigation of mechanism for formation of **14** and **16**.

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