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A mild and regioselective synthesis of α-fluoroketones *via* gold and Selectfluor partnership

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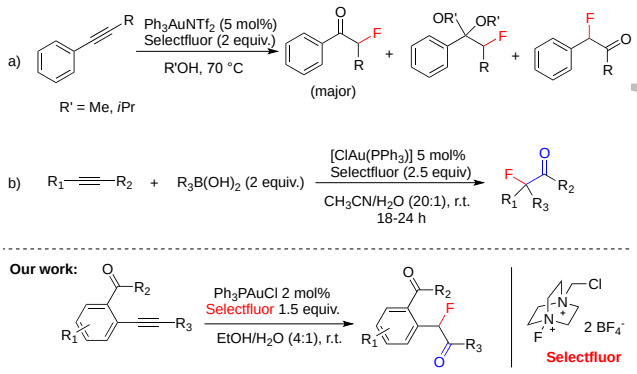
Abstract. An efficient, mild and rapid synthesis of α-fluoroketones has been developed, *via* a fruitful association between gold and Selectfluor starting from aldehyde-yne and alkynylaryl ketone derivatives. Several functionalized and synthetically highly valuable α-fluoroketones (21 compounds, up to 92%) were isolated in good to excellent yields *via* a remarkable regioselective oxyfluorination reaction in EtOH/H_2O at room temperature. We have shed some light on parts of the mechanism by reacting diphenylacetylene and aldehyde-yne with or without Selectfluor. The reaction most presumably occurs *via* a sequential gold-catalyzed regioselective hydration followed by the α-fluorination reaction, but the presence of aldehyde moiety is crucial for the reactivity of alkyne function. The fluoroketones were efficiently transformed to 4-fluoroisoquinolines (9 compounds, 82-95%) of high pharmaceutical interest.

Keywords: α-fluoroketones; oxyfluorination; gold; selectfluor; 4-fluoroisoquinoline

Introduction

In the past decade, gold catalysis keeps an exponential growth and has become a fundamental and innovative synthetic tool for the construction of carbon-carbon or carbon-heteroatom bonds.[1,2] Moreover, unique activation modes presented by gold associated with fluorinated species have been developed in recent years, arising to new methodologies in fluoroorganic chemistry.[3] Due to the high interest of fluorinated compounds in organic, medicinal and biological chemistry,[4] developing efficient strategy to incorporate fluorine atom into organic molecules is very important. The fruitful association of gold and Selectfluor[5] was first reported by Gouverneur's group in 2008[6] and then unveiled a new area in gold catalysis.[5,7] In 2010, Nevado's group opened up a new method to synthesize α-fluoro acetals and α-fluoro ketones, by reacting terminal and internal alkynes with alcohols, in the presence of catalytic gold complex and Selectfluor, leading to the corresponding fluorinated products depending on the reaction conditions (Scheme **1a**).[8] Hammond and co-workers found other synthetic methods concerning hydration of alkynes, in the presence of gold/Selectfluor and organoboronic acids, to give α-substituted α-fluoroketones (Scheme **1b**).[9] It remains challenging to develop regioselective synthesis of α-fluoroketones via gold-catalyzed process under mild conditions.[10] Herein, following our interest in aldehyde-yne cycloisomerization[11] and in gold/Selectfluor association,[12] we wish to describe our preliminary results on an unprecedented mild synthetic strategy by which a variety of α-fluoroketones were synthesized efficiently starting from aldehyde-yne derivatives and alkynylaryl ketones in the presence of gold/Selectfluor partnership.



Scheme 1. Reactions of alkyne derivatives *via* gold-catalyzed fluorination.

Results and Discussion

We started with optimizing the experimental conditions by using the model reaction of 2-(*o*-tolylethynyl)benzaldehyde (**1a**) with Selectfluor, as disclosed in Table 1. Initially, the effects of different

Table 1. Conditions optimization for the synthesis of **2a**.[a)]

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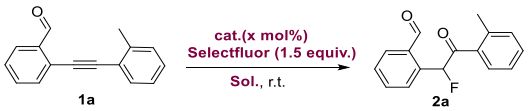
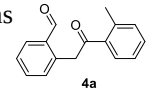
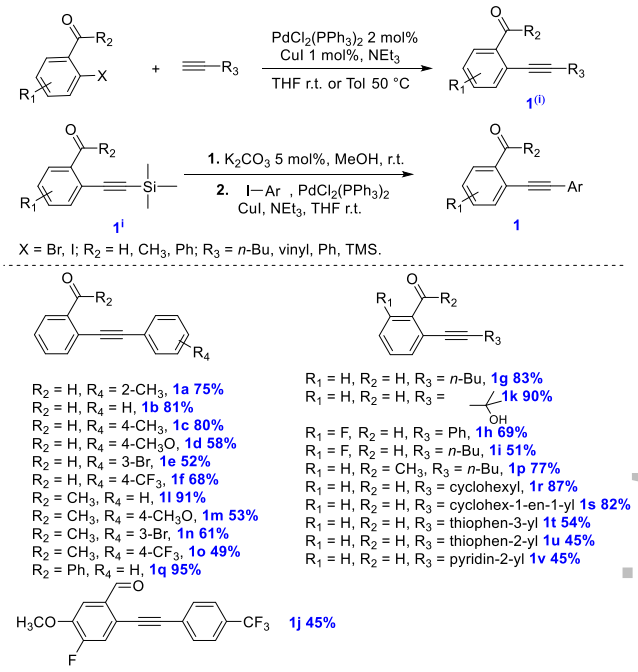


Entry	Catalyst (mol%)	Solvent (v/v)	Time (h)	Yield (%)[b]
1	Ph_3PAuCl (5)	EtOH/ H_2O 4/1	4	90
2	$Ph_3PAuNTf_2$ (5)	EtOH/ H_2O 4/1	4	90
3	$PicAuCl_2$ (5)	EtOH/ H_2O 4/1	4	18
4	$KAuCl_4$ (5)	EtOH/ H_2O 4/1	4	58
5	AuCl (5)	EtOH/ H_2O 4/1	4	traces
6	$PdCl_2$ (5)	EtOH/ H_2O 4/1	4	51
7	$PtCl_2$ (5)	EtOH/ H_2O 4/1	4	traces
8	$InCl_3$ (5)	EtOH/ H_2O 4/1	4	traces
9	$CuCl_2$ (5)	EtOH/ H_2O 4/1	4	traces
10	CuI (5)	EtOH/ H_2O 4/1	4	traces
11	Ph_3PAuCl (1)	EtOH/ H_2O 4/1	12	82
12	Ph_3PAuCl (2)	EtOH/ H_2O 4/1	6	88
13	Ph_3PAuCl (0)	EtOH/ H_2O 4/1	6	traces
14[c]	Ph_3PAuCl (2)	EtOH/ H_2O 4/1	6	0
15[d]	Ph_3PAuCl (5)	EtOH/ H_2O 4/1	4	85
16[e]	Ph_3PAuCl (5)	EtOH/ H_2O 4/1	4	81
17[f]	Ph_3PAuCl (5)	EtOH/ H_2O 4/1	16	79
18	Ph_3PAuCl (5)	DCM/ H_2O 4/1	5	13
19	Ph_3PAuCl (5)	DMF/ H_2O 4/1	5	77
20	Ph_3PAuCl (5)	CH_3CN/H_2O4/1	5	60
21	Ph_3PAuCl (5)	THF/ H_2O 4/1	5	16
22	Ph_3PAuCl (5)	THF/ H_2O 4/1	24	39
23	Ph_3PAuCl (5)	EtOH/ H_2O 1/1	4	83
24	Ph_3PAuCl (5)	EtOH/ H_2O 0/1	24	71
25[g]	Ph_3PAuCl (5)	EtOH/ H_2O 4/1	2	0[h]
26[g]	$Ph_3PAuNTf_2$ (5)	PhMe/ H_2O 4/1	5	0[h]

[a] Reaction conditions: 0.3 mmol of **1a**, 1.5 equiv. Selectfluor in 3 mL of solvents at room temperature. [b] Isolated yield. [c] No Selectfluor was added. [d] Selectfluor (1.0 equiv.) was added. [e] Selectfluor (2.0 equiv.) was added. [f] Using NFSI (1.5 equiv.) instead of Selectfluor. [g] No Selectfluor and 80 °C. [h] Compound **4a** was obtained in 14% and 70% respectively (determined by 1H NMR analysis using 3,4,5-trichloropyridine as the internal standard).



metal salt catalysts were investigated in entries 1-10. Ph_3PAuCl and $Ph_3PAuNTf_2$ exhibited good catalytic activity for this fluorination reaction, giving 90% yields. Comparatively, the gold catalysts $PicAuCl_2$, $KAuCl_4$ and AuCl displayed lower catalytic activity to access 2-(1-fluoro-2-oxo-2-(*o*-tolyl)ethyl) benzaldehyde **2a**. Conducting the reaction in the presence of $PdCl_2$, $PtCl_2$, $InCl_3$, $CuCl_2$ and CuI gave no



Scheme 2. Structures of aldehyde-ynes and alkynylaryl ketones compounds **1**.

conversion in most cases except with $PdCl_2$ which led to 51% yields of the product. Gratifyingly, decreasing the amount of Ph_3PAuCl to 2 and 1 mol% allowed the formation of the desired derivative in good yields (entries 11-13). The investigation on the amount of Selectfluor (entries 14-16) indicated that 1.5 equivalents was the best compromise to have the highest yields. The use of 1.5 equivalents of NSIF was possible and gave the corresponding fluoro adduct **2a** in 79% yield, despite a much longer reaction time (entry 17). The reaction conditions were explored in various solvents such as DCM, DMF, CH_3CN, THF, H_2O (entries 18-26) and in different solvent ratios. As control experiments, without Selectfluor (entries 25-26), the reaction led to the ketoaldehyde **4a** in 14% and 70% yields in EtOH/H_2O and toluene/H_2O respectively. Interestingly, the best results for oxyfluorination reactions were therefore obtained in green solvents such as H_2O or EtOH/H_2O mixture.

We therefore selected the reaction conditions implying 2 mol% Ph_3PAuCl and 1.5 equivalents Selectfluor in a 4/1 EtOH/H_2O ratio at room temperature. With a set of optimized conditions in hand, we examined the scope of the gold/Selectfluor promoted α-fluorination reaction as shown in Scheme 3. For this purpose and to broaden the functionalities amenable on the *ortho*-functionalized alkynes, we synthesized various aldehyde-ynes, alkynylaryl and alkynylheteroaryl ketones **1a-1v** by the classical Sonogashira coupling reactions (Scheme 2).[11] The generality and the substrate scope of aldehyde-yne derivatives and alkynylaryl ketones is described in Scheme 3. The 2-(phenylethynyl)benzaldehyde (**1b**) was obtained in good 85% yield. Then aldehydes bearing electron-donating groups (*ortho*-methyl-substituted, *para*-methyl-substituted and *para*-

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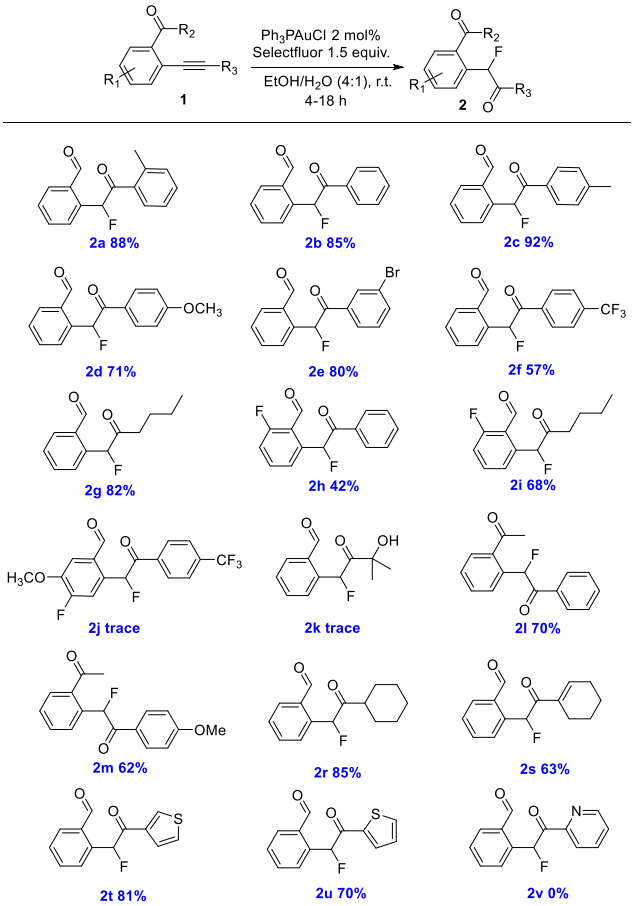
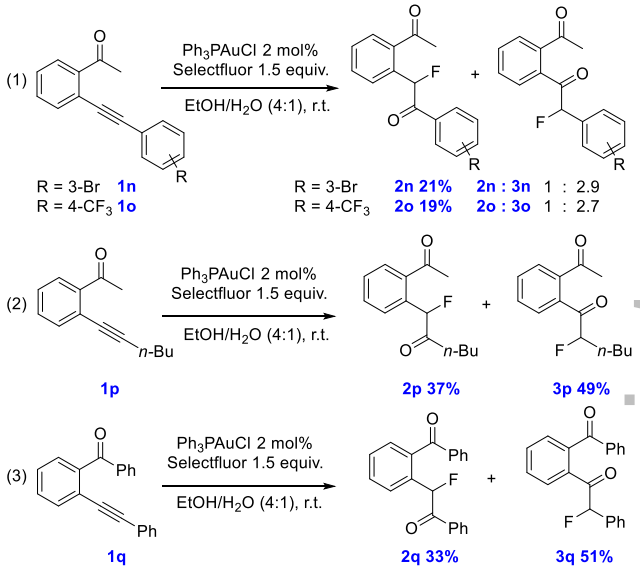
methoxy-substituted) on the phenyl ring were efficiently transformed to the corresponding products **2a**, **2c-d** in 71% - 92% yields.



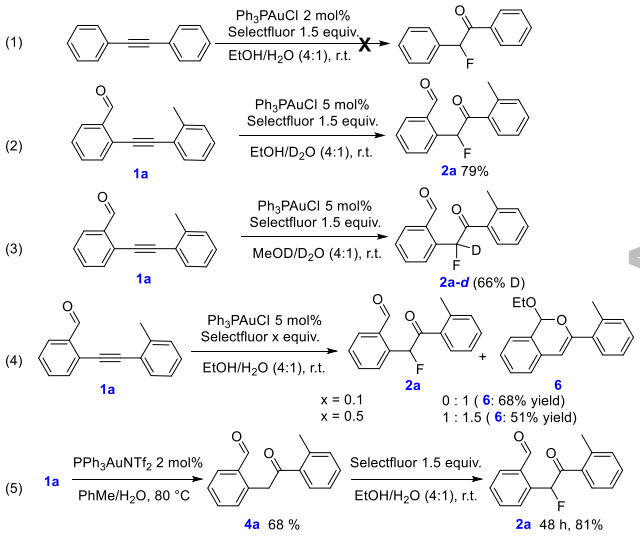
Scheme 3. Scope of synthesis of α-fluoroketones **2**.

The substrates functionalized by electron-withdrawing groups such as *meta*-bromo and *para*-CF_3, reacted smoothly with gold and Selectfluor, giving products **2e-f**. Furthermore, when the aromatic alkyne was switched by aliphatic alkyne (**1g**), the derivative **2g** was nicely isolated in good yield. Some limitations were observed for 4-fluoro-5-methoxy-2-((4-(trifluoromethyl)phenyl)ethynyl) benzaldehyde (**1j**) and 2-(3-hydroxy-3-methylbut-1-yn-1-yl) benzaldehyde (**1k**), which gave only traces of the desired compounds, unexpectedly in the case of **1j** and which could be explained by a deactivative complexation of alcohol with gold for **1k**. Anticipating the importance of the carbonyl aldehyde moiety and to extend the scope of the reaction, we also studied the reactivity of substituted ketones. Gratifyingly, 1-(2-(phenylethynyl)phenyl)ethan-1-one (**1l**) reacted well, giving **2l** in 70% yield. The presence of electron-donating group on the aryl of the alkyne moiety was amenable under the reaction conditions (**2m**, 62% yield). The reactivity of cycloalkyl and cyclohexenyl derivatives **1r-s** was also challenged and the oxyfluorination process led to fluoroderivatives **2r** and **2s** in 85% and 63% isolated yield respectively. The reaction conditions were compatible with heterocycles such as thiophenyl adducts **1t-u**, but not with pyridine-functionalized alkynes. The sulfur-containing fluoroketones **1t** and **1u** were obtained in high yields.



Scheme 4. Examples of α-fluoroketones **2** and β-fluoroketones **3**.

We then decided to compare the reactivity of **1e-f** and their Me-ketone analogues **1n-o** (Scheme 4). In these cases, both α- and β-fluoro regioisomers **2n** and **3n** as well as **2o** and **3o** were identified in a 1:2.9 and 1:2.7 ratio (determined by ^{19}F NMR), but the α-fluoro adducts **2n** and **2o** were the only possible isolated isomers in 21% and 19% yields respectively (Eq. 1, Scheme 4). When switching from aryl to alkyl group, both isomers could be separated and identified, the functionalized diketones being isolated in 37% and 49% (Eq. 2, Scheme 4).



Scheme 5. Mechanistic studies.

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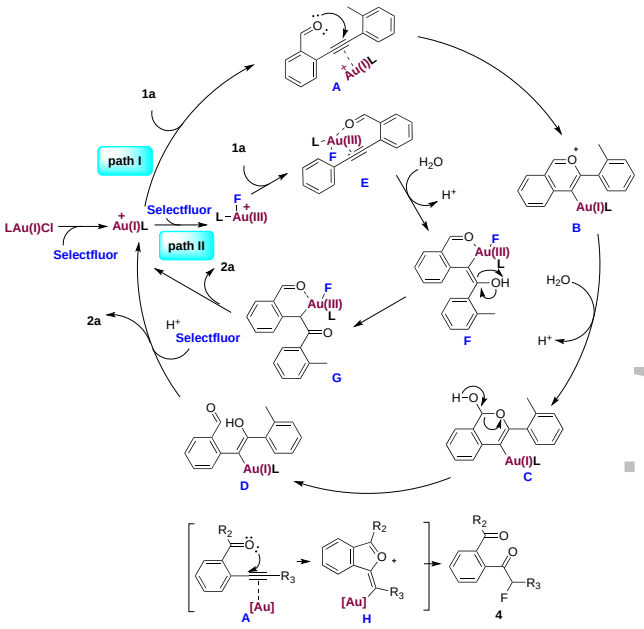
Similarly, the phenylketone **1q** nicely reacted in the presence of the gold/Selectfluor association and led to a mixture of isomers **2q** and **3q** in 33% and 51% isolated yields (Eq. 3, Scheme 4). The lack of regioselectivity could be encountered by a weakened regional selection effect, most probably due to electronic features of the substrates (*vide infra*). These four striking examples of access to β-fluoroketones **3** according to an abnormal effect phenomenon prompted us to study the mechanism of the whole process. In order to shed light on the mechanism, we performed controlled experiments in the presence of non-functionalized alkyne and in the presence of deuterated solvents. When 1,2-diphenylethyne was used instead of substrate **2a** under the standard conditions, no desired product 2-fluoro-1,2-diphenylethan-1-one was observed, clearly suggesting that *ortho*-CHO moiety is a key group in this reaction and that no reaction occurs at room temperature (Scheme 5, Eq. 1). Considering the literature on the reactivity of *ortho*-alkynylarylaldehydes described by us and others and the very mild conditions, we were not surprised by such observation. This example once again shows that aldehyde moiety participates to the whole process by addition to the activated alkyne (Scheme 6). In the presence of D_2O (Scheme 5, Eq. 2), non-deuterated product **2a** was the only isolated derivative, which can be correlated with the proton exchange between EtOH and D_2O. Therefore, using a mixture of MeOD and D_2O, we were pleased to isolate the deuterated fluoro derivatives **2a-*d*** (Scheme 5, Eq. 3). We also evaluated the importance of the partnership between PPh_3AuCl and Selectfluor (Scheme 5, Eq. 4) in order to compare with the Nevado's system. When the reaction was conducted in the presence of 10 mol% of Selectfluor, the major compound was the ketal **6**,[1-2] resulting from classic alkoxycyclization of **1a**. Increasing the amount of Selectfluor gave rise to the formation of the fluoro derivative **2a** with the ether **6**.

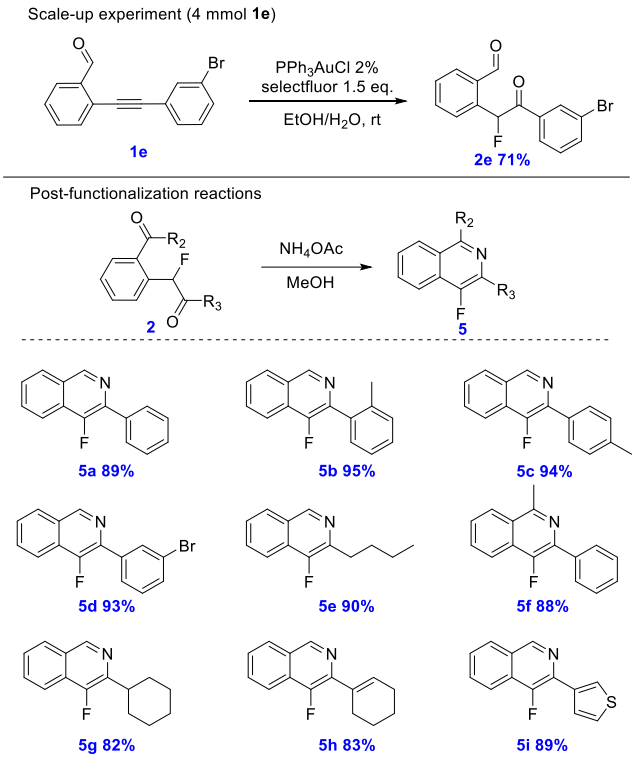
The last crucial experiment was the analysis of the fluorination step compared to the hydration step. As anticipated,[13] the reaction of **1a** in the presence of gold catalyst and water at high temperature afforded the ketone **4a** in 68% yield (Scheme 5, Eq. 5). We slightly modified the reaction conditions from Table 1, and by using toluene instead of EtOH, the ketoaldehyde **4a** was isolated in good yield. Importantly, the reaction of **4a** in the presence of 1.5 equivalents of Selectfluor afforded the fluoro compound **2a**, but in an increasing time compared to the one-pot reaction of **1a** with gold and Selectfluor. We can therefore conclude that, as expected,[14] the fluorination step can occur on the ketoaldehyde **4a** without gold catalyst, but this reaction is kinetically very slow, which makes us propose the following mechanism (Scheme 6). It is well accepted since the seminal work from Belmont, Yamamoto and Abbiati,[15] that in the presence of a Lewis acid catalyst,[9,12b,15,16] the reaction goes *via* π-activation of alkyne **1a** by coordination of the Lewis acid to the triple bond (**A**) and subsequent 6-*endo*-dig attack of the carbonyl moiety leading to isobenzopyrylium intermediate **B**.[17]



Scheme 6. Proposed reaction mechanism.

This specie was identified as highly reactive towards nucleophilic addition to form metal-alkenyl intermediate of type **C**.[10,11,15] We can propose a similar mechanism, based on the nucleophilic addition of water on the pyrylium intermediate. Intermediate **C** is very unstable and most probably evolves towards opening of ketal to form enol **D**. Then two scenarios may occur, the first one being the protodemetalation step of metallic intermediate **C** giving **4a**, which will then be fluorinated as showed in Scheme 5. An alternative pathway, may be the direct Au-F interaction as proposed by Toste and Zhang,[18] and Hammond and Xu in 2010,[9] that would lead to a Au^{III} intermediate, giving intermediate **E** by oxophilic activation of aldehyde. Hydration of **E** would give intermediate **F** which would evolve towards a σ-gold complex **G** and then after a reductive elimination would give **2a**. This second possibility is attractive considering the kinetic of the whole process and the outcome of the reaction in the presence of PPh_3AuCl without Selectfluor (Table 1, entry 25). Interestingly, in the case of alkynylaryl ketones **1n-1q**, the intermediate **A** would give intermediate **H**, according to a 5-*exo*-dig cyclization, which was observed in the literature in the presence of a base or electron-withdrawing groups on the R_3 moiety.[19] The 5-*exo*-dig cyclization was also observed in the case of the hydroamination of *ortho*-alkynyl benzylcarbamates by Catalián and co-workers.[20] The substitution of the benzylic position by electron-withdrawing groups allowed an increase in the 5-*exo* isomer compared to 6-*endo* one.[20] Intermediate **H** is more stable than **B** in these cases, which explains the formation of the other regioisomers **4** according to the same final elementary

steps (addition of water, opening of the intermediate and fluorination).



Scheme 7. Scale-up experiment and post-functionalization reactions. Reaction conditions: 0.2 mmol **2** and 3 equiv. NH_4OAc in 2 mL MeOH 2 - 4 h at room temperature.

The usefulness of the oxofluorination process could be also established by performing a scale-up experiment and post-functionalization (Scheme 7). Rewardingly, the gram-scale transformation of compound **1e**, a valuable scaffold for post-functionalization through palladium-catalyzed cross-coupling reactions, led to the multifunctionalized adduct **2a** in 71% isolated yield. Interestingly, we could finally demonstrate that α-fluoroketones **2** may serve as a key platform for the preparation of fluoro-isoquinoline of high pharmaceutical interest.[21, 22] The reaction of α-fluoroketones **2** in the presence of 3 equivalents of NH_4OAc[23] gave cleanly, efficiently and in a short time the corresponding 4-fluoro-isoquinoline compounds **5a-5i**. The excellent isolated yields ranged from 82% to 95%, which makes this approach very competitive to other methods.[24]

Conclusion

In conclusion, we have therefore extended the methodology of the gold-catalyzed domino reactions by studying the oxofluorination process. An efficient and practical route for the preparation of functionalized α-fluoroketones was optimized in the presence of gold catalyst associated to Selectfluor partner in green solvent under mild conditions. The α-fluoroketones were synthesized in good to excellent yields starting from simple aldehyde-yne or ketone-yne derivatives as substrates. We studied the scope and limitations and highlighted the influence of each part of the carbonyl-yne platform. The oxofluorination was fully regioselective in the case of aldehyde-yne derivatives whereas the opposite regioselectivity was observed in the case of ketone-yne adducts. We have shed some light on parts of the mechanism showing that the oxofluorination process is a domino process which implies the formal hydration of the triple bond before the fluorination step. The prominent advantages of our reaction include low catalyst loading, base or acid free and green solvent under mild conditions. We have also broadened the scope of this method by showing its applicability on a larger scale and by preparing challenging 4-fluoroisoquinoline derivatives in excellent yields. Further studies will focus on practical and industrial applications of this straightforward and highly atom economical process.

Experimental Section

Synthesis of α-fluoroketones compounds, general procedure: In 10 mL round-bottomed flask, the substrate **1** (0.4 mol, 1 equiv.) and Selectfluor (1.2~1.5 equiv.) in 4 mL $EtOH/H_2O$ (v/v 4/1), then added catalyst Ph_3PAuCl (4 mg, 2 mol%). The mixture was stirred at room temperature until completion (4-18 hours, TLC analysis). The solvent was removed under reduced pressure, extracted from DCM/H_2O several times, washed with brine. The organic phase was dried over $MgSO_4$, filtered and evaporated. The crude product was purified by silica-gel column chromatography (petroleum ether/ethyl acetate: 80:20~92/8) to afford the corresponding fluoro product.

Synthesis of 4-fluoroisoquinoline compounds, general procedure: In a flask, to a methanol solution (2 mL) of product **2** (1.0 equiv, 0.2 mmol), NH_4OAc (47.3mg, 3 equiv) was added under air condition. The reaction mixture was stirred at room temperature for 2~4 hours. After completion of the reaction (monitored by TLC), the organic solvent was removed under vacuum, and the residue was directly purified by silica gel column with petroleum ether/ethyl acetate around 8:2~9/1 to afford products.

Acknowledgements

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UPDATE

A mild and regioselective synthesis of α-fluoroketones *via* gold and Selectfluor partnership

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