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One-Pot Gold-Catalyzed Aminofluorination of Unprotected 2-Alkynylanilines

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ABSTRACT

A tandem gold(I)-catalyzed aminocylization/fluorination and a two-step, one-pot gold(III)-catalyzed cyclization/electrophilic fluorination provide a convenient and general method for the synthesis of 3,3-difluoro-2-substituted-3*H*-indoles in good yield under mild conditions. Extension of the procedure to the synthesis of 2-aryl-3-fluoro-1*H*-indoles is described. The reaction proceeds smoothly in green ethanol and does not require any base, acid, or *N*-protective group.

Introducing fluorine into molecules represents a major challenge in organic synthesis.[1] The substitution of hydrogen with fluorine can lead to a dramatic impact in the physicochemical and biological properties of organic compounds, and utilization of fluorine derivatives spans areas as diverse as pharmaceuticals, agrochemicals, and polymers.[2] In particular, strategic fluorination of heterocyclic compounds has become an ever more important weapon in the armamentarium of medicinal chemistry.[3]

Modification of the indole structure continues to attract great interest from organic chemists reflecting its importance as an ubiquitous skeleton of pharmaceuticals and bioactive natural products.[4] Several studies have been dedicated to the electrophilic substitution in the indole core with fluorinating agents, and the methodologies available allow the introduction of −F to positions 2 or 3 (starting from corresponding trimethylstannyl indoles)[5] to positions 4,[6] 7,[7] and to various positions of the benzenic

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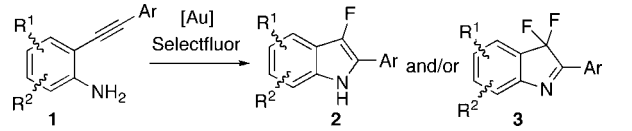
ring.[8] Few other studies revealed the access to C3 mono- or difluorinated indole derivatives. The syntheses of 3-substituted 3-fluorooxindoles,[9] 3,3-difluoroindoles or indolines,[10] or *trans*-2,3-difluoro-2,3-dihydroindoles, monofluoroindole derivatives, or monofluoroindolines[11] have been described in the presence of NFSI, DAST, and Selectfluor. To the best of our knowledge, the synthesis of 2-substituted 3-fluoroindoles has not been previously described. Our continuing interest in the synthesis of indole derivatives by one-pot processes[12] and in the formation of carbon−heteroatom bonds via Au-catalyzed π-activation of alkynes[13] prompted us to investigate an alternative approach to 3,3-difluoro-2-arylindolines **3** with better flexibility starting from unprotected o-alkynylanilines **1**. Moreover, we explored the extension of the procedure toward the unprecedented synthesis of 3-fluoro-2-aryl-indoles **2** (Scheme 1). We wish to report herein our preliminary results.

First, the readily available 2-[[4-(methoxy)phenyl]ethynyl]-aniline **1a** was chosen as a model substrate and Selectfluor as a source of electrophilic fluorine to carry out the desired cyclization−fluorination sequence. Indeed, Selectfluor has shown very interesting activity in the Au-catalyzed aminofluorination of alkynes to prepare fluorinated pyrrolidines[14] and pyrazoles.[15,16]

The results of Table 1 show that the reaction of **1a** with an excess of Selectfluor and water in CH_3CN at room temperature in the absence of any catalyst failed to give the

Scheme 1



desired C3 fluorinated indole derivatives ruling out their formation by a direct electrophilic fluorocyclization process[14,17] (Table 1, entry 1). Under these conditions, a fast degradation of the starting *N*-unprotected 2-alkynylaniline **1a** was observed. When the same reaction was carried out in the presence of $Ph_3PAuNTf_2$[18] (10 mol % of the commercially available dimeric form), the formation of the difluorinated indoline **2a** was observed although in a modest 35% yield (Table 1, entry 2). Subsequently, various parameters such as solvents[19] and the amount of water[10b,20] were screened to improve the reaction efficiency. The presence of a larger amount of water, e.g., 100 equiv (Table 1, entry 3), led to a decrease of the yield as it may speed up the protodeauration of indolylgold intermediate species (42% of the corresponding 2-substituted indole was detected). Ethanol has proven to be the best choice for the reaction among solvents screened so far (MeCN, dioxane, and acetone, Table 1, entries 3−6). Satisfyingly, the yield of **3a** was increased to 75% by using EtOH as the reaction medium (Table 1, entry 4). By contrast with the results observed in the gold(I)-catalyzed tandem aminofluorination of 1-phenyl-2-(4-phenylbut-3-yn-2-ylidene)hydrazine to give the corresponding fluorinated pyrazole, the addition of base to the reaction mixture resulted detrimental and we failed to obtain **3a** under the presence of $NaHCO_3$[16] Other gold catalysts such as AuCl, $AuCl_3$, and $NaAuCl_4$ (Table 1, entries 7−9) were tested and allowed the formation of **2a** in 38−56%. In addition, it was found that other transition-metal catalysts such as $PdCl_2$, $PtCl_2$, $CuCl_2 \cdot 2H_2O$, $RuCl_3 \cdot 2H_2O$, or $AgNTf_2$ were ineffective. Although less effective in the model study, we selected the cheaper $NaAuCl_4 \cdot 2H_2O$ catalyst that previously, in our hands, allowed a mild and green procedure for the synthesis of indoles from 2-alkynylanilines[17] and explored the Au(III)-catalyzed cyclization of 2-alkynylanilines combined in a one-pot procedure with the C3 fluorination of the in situ formed 2-substituted indole by Selectfluor.

A one-pot procedure was used with the aim of accomplishing efficiently the process and avoiding the use of time- and resource-consuming workup and purification procedures.[21] Alkynes **1** were converted into the corresponding 2-substituted indoles in EtOH at room temperature by using 5 mol % of $NaAuCl_4 \cdot 2H_2O$. Selectfluor (3 equiv) was then added

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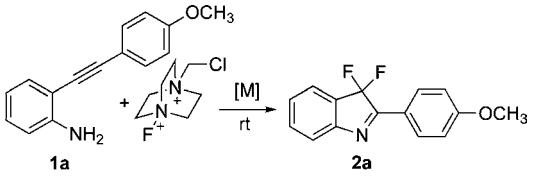
Table 1. Optimization of Reaction Conditions for the Tandem Aminodifluorination of 2((4-Methoxyphenyl)ethynyl)aniline **1a**[a]



1a **2a**

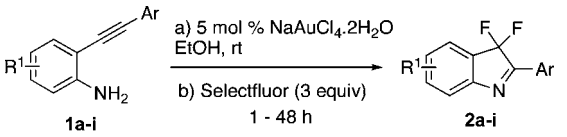
entry	[M] 10 mol %	solvent (H_2O x equiv)	time (h)	yield[b] (%)
1		CH_3CN (10)	3	
2[c]	$Ph_3PAuNTf_2$	CH_3CN (10)	3	35
3[c]	$Ph_3PAuNTf_2$	CH_3CN (100)	3	17
4[c]	$Ph_3PAuNTf_2$	EtOH (100)	1.5	75
5[c]	$Ph_3PAuNTf_2$	1,4-dioxane (100)	2	0
6[c]	$Ph_3PAuNTf_2$	acetone (100)	2	0
7	AuCl	EtOH (100)	2	56
8	$AuCl_3$	EtOH (100)	2	38
9	$NaAuCl_4$	EtOH (100)	0.25	45

[a] Conditions: 0.45 mmol of alkyne **1a** and 2.5−3 equiv of Selectfluor, 10 mol % of [M], 0−100 equiv of water in 4.5 mL of solvent at room temperature. [b] Isolated yields. [c] The formation of the aminocylization derivative 2-(4-methoxyphenyl)-1*H*-indole **4a** was observed (42% yield).

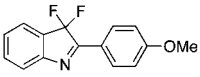
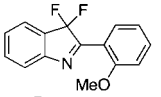
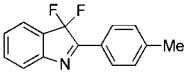
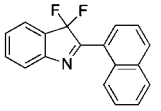
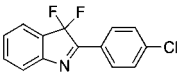
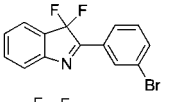
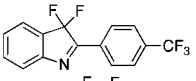
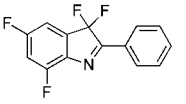
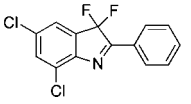
when full conversion of the gold(III)-catalyzed cyclization of **1** was observed. The results are summarized in Table 2. A variety of alkynyl derivatives **1** underwent cyclization/fluorination smoothly, displaying a broad substrate compatibility. It was found that alkynyl derivatives **1** bearing both electron-rich and electron-poor aryl-substituted moieties furnished the corresponding products **2** in moderate to good yields (57−86%). *o*-Substituent tolerance was also proved as exemplified by the cyclization/functionalization of *o*-methoxy- or naphthyl-substituted derivatives (Table 2, entries 2 and 4). The in situ cyclization of 2-alkynylanilines has the advantage that the resulting products, 2-substituted indoles, are easily functionalized by electrophilic aromatic substitution at position 3 without isolation and purification of the 3-unsubstituted indole intermediate.[10] The difluoro or dichloro substitutions in the *ortho*- and *para*-positions of the anilines were tolerated (Table 2, entries 8 and 9). Interestingly, the polyfluorinated indoline **2h** was isolated in high yield (Table 2, entry 8). It is noteworthy that, in the presence of the electron-withdrawing groups in the aniline ring, the cyclization step was to slow at room temperature and the reactions were therefore carried out in EtOH at reflux. The increase of the reaction temperature exhibited benefical effects also in the presence of an *ortho* substituent group in the aryl moiety of **1**.

The isolation of the monofluorinated product **3f** together with the difluoronitated **2f** prompted us to modify the standard reaction conditions trying to access selectively to monoflurinated derivatives. Gratifyingly, by only using 1.1 equiv of Selectfluor, the desired 3-fluoro-2-arylindoles **2e**−**g** were isolated in satisfactory yield (Scheme 2). Whereas a mixture of mono- and difluorinated adducts was obtained in the case of 3-Br- and 4-CF_3-substituted arylakynes **1f** and **1g**, the monofluorinated indole **3e** was isolated in 75% yield.

Table 2. Substrate Scope*



1a-i **2a-i**

entry	R^1	Ar	product		t (h)	yield (%)[a]
1	H	4-$MeOC_6H_4$		**2a**	48	74
2[b]	H	2-$MeOC_6H_4$		**2b**	1	60
3	H	4-MeC_6H_4		**2c**	24	83
4	H	1-naphthyl		**2d**	43	76
5	H	4-ClC_6H_4		**2e**	24	67
6	H	3-BrC_6H_4		**2f**	26	65[c]
7	H	4-$CF_3C_6H_4$		**2g**	8	67
8[b]	4,6-F_2	C_6H_5		**2h**	5	86
9[b]	4,6-Cl_2	C_6H_5		**2i**	4	85

* Reaction conditions: 1 equiv of diyne, $NaAuCl_4 \cdot 2H_2O$ (5 mol %) in EtOH (0.1 M), then Selectfluor (3 equiv) was added to the reaction mixture. [a] Isolated yield. [b] Reflux. [c] 13% of the monofluorinated indole was also isolated.

For substituted anilines bearing a chloro or fluoro group, the procedure allowed the exclusive formation of **3h** and **3i** in modest to good yields.

On the basis of the previous literature,[22] since the gold(I) complex could be oxidized into the gold(III) complex in the presence of Selectfluor[23] and the gold(III) complex also catalyzed the reaction, two main mechanistic manifolds regarding the tandem gold(I)-catalyzed aminofluorination of **1** can occur (Scheme 3). First, the reaction may proceed via a gold(I) catalytic cycle via intermediates **A** and **B**. Intermediate **B** could be either oxidized into the gold(III)

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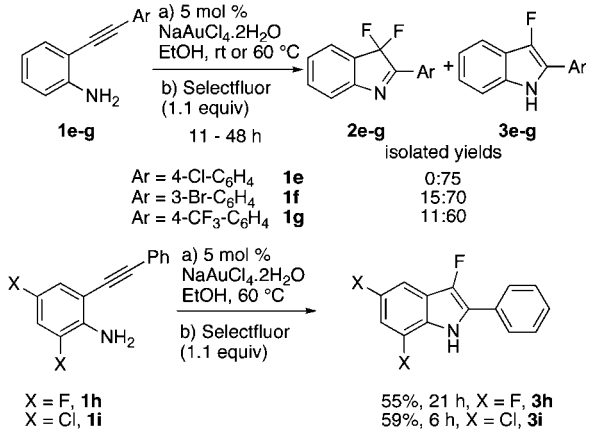
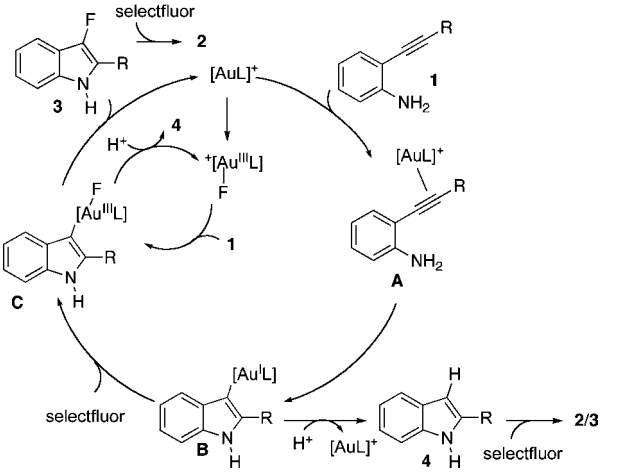
Scheme 2



complex **C** in the presence of Selectfluor or protodemetalated to form indole **4**. Upon reductive elimination of intermediate **C**, the gold(I) catalyst is regenerated and the 2-substituted-3-fluoro indole **3** is formed.[24] A second mechanistic pathway involving redox Au(I)/Au(III) catalytic cycle may also be possible, leading after oxidation of Au(I) catalyst to intermediate **C**.[25] Moreover the 2-substituted indole derivative **4** derived by the electrophilic protodeauration of the indolyl gold(I)[26] or indolyl gold(III) species[27] might undergo an uncatalyzed monofluorination[21] reaction which will be followed by difluorination[28] in the presence of an excess of Selectfluor.

Scheme 3. Mechanism Rationale



In conclusion, the unprecedented gold-catalyzed aminofluorination of unprotected 2-alkynylanilines was investigated. An alternative approach to 3,3-difluoroindole derivatives with better flexibility over the previously described procedures has been developed. A two-step, one-pot gold(III)-catalyzed cyclization/electrophilic fluorination was achieved in green ethanol and allowed the synthesis of 3,3-difluoro-2-substituted-3*H*-indoles in good yield under mild conditions. Extension of the procedure to the synthesis of 2-aryl-3-fluoro-1*H*-indoles was explored. The methodology is simple to perform and requires use of neither bases, acids, nor *N*-protective groups. Further investigation is in progress to direct the tandem gold-catalyzed oxidative cycloamination reaction toward different indoles.[29]

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Supporting Information Available. Experimental procedures and characterization data of new products **1f**,**I**, **2a**–**i**, and **3e**–**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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