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A Novel Synthesis of Fluorinated Pyrazoles via Gold(I)-Catalyzed Tandem Aminofluorination of Alkynes in the Presence of Selectfluor

Jianqiang Qian, Yunkui Liu,* Jie Zhu, Bo Jiang, and Zhenyuan Xu*

State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology, Hangzhou 310014, People's Repubilc of China

ykuiliu@zjut.edu.cn; greensyn@zjut.edu.cn

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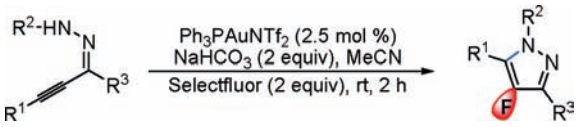
ABSTRACT



A mild and efficient protocol for the synthesis of fluorinated pyrazoles has been developed via gold(I)-catalyzed tandem aminofluorination of alkynes in the presence of Selectfluor. This method offers a broad substrate scope.

Pyrazoles constitute an important class of N-heterocycles, exhibiting unique pharmaceutical and biological activities.[1] Recently, the fluorine-containing pyrazoles have received special attention due to their interesting biological properties serving as precursors for pharmaceuticals and pesticides.[2] However, the number of published routes to these compounds is fairly limited mainly due to the difficulty of introducing a fluorine atom into heterocycles.[2,3] The representative approaches to fluoropyrazoles include direct ring fluorination using electrophilic fluorinating reagents,[2a,b] cyclocondensation reactions of fluorinated diketo or monoketo compounds with substituted hydrazines,[2c−e] diazotization of aminopyrazoles followed by photochemical decomposition of diazonium tetrafluoroborates,[2f] direct nucleophilic displacement of bromine by fluorine in 4-bromopyrazole derivatives,[2g] monofluorination of β-methylthio-β-enaminoketones using Selectfluor followed by condensation of the resulting monofluorinated enaminoketones with hydrazines,[2h] etc. Unfortunately, in most cases, there are one or more limitations associated with these procedures, such as low yields, multiple steps, narrow scope of substrates, harsh reaction conditions, using dangerous reagents, or not easy availability of the starting materials. Therefore, there is high demand to develop mild and efficient methods with broad substrate scope for the synthesis of fluoropyrazoles.

On the other hand, transition-metal-mediated C−F bond formation has recently drawn growing attention and has become a powerful tool for the construction of

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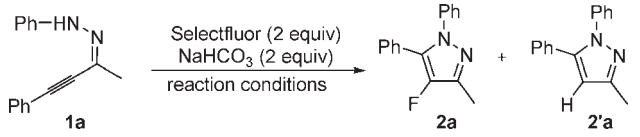
organic fluoro compounds.[4−7] In this context, palladium and gold are among the most promising metals for C−F bond formation. While palladium has had much success in the formation of an aromatic C−F bond[5a−f] and less success in the fluorination of alkenes,[5g,h] gold has had major success in the fluorination of alkynes.[6] For example, in 2007, Sadighi and co-workers reported a gold(I)-catalyzed hydrofluorination of alkynes using $Et_3N \cdot 3HF$ as a nucleophilic source of fluorine.[6b] Following the same principle, Miller et al. achieved a regio- and stereoselective hydrofluorination of alkynes by using carbonyl groups as the directing group.[6c] In 2008, Gouverneur pioneered an alternative approach for the fluorination of alkynes by combination of a gold(I) catalyst with an electrophilic fluorine source, such as Selectfluor.[6d] Then, Gouverneur, Nevado, and Hammond et al. successfully applied this strategy for 1,3-acyloxy rearrangement/fluorination of propargyl acetates,[6e,f] alkoxylation/hydration/fluorination of alkynes,[6g] and arylation/hydration/fluorination of alkynes.[6h] These studies have enabled chemists to develop direct and efficient ways to form the C−F bond based on ubiquitous alkyne moieties as backbones involving a redox Au(I)/Au(III) catalytic cycle,[8,9] yet the examples remain very sparse.[6] Herein, we report the first gold-catalyzed aminofluorination[10] of alkynes to give fluorinated pyrazoles at room temperature as part of our studies on the construction of heterocycles via gold-catalyzed tandem reactions.[11−13]

Table 1. Optimization of Reaction Conditions[a]



entry	reaction condition	**2a**/**2′a**[b]	yield (%, **2a**)[c]
1	AuCl, MeCN	1:1.2	12
2	Ph_3PAuCl, MeCN	5.3:1	76
3	**$Ph_3PAuNTf_2$, MeCN**	**6.2:1**	**81**
4	Ph_3PAuCl/AgOTf, MeCN	3.8:1	55
5	$Ph_3PAuCl/AgSbF_6$, MeCN	1:1.3	39
6	Ph_3PAuCl/AgF, MeCN	5.9:1	61
7	Ph_3PAuCl/AgCN, MeCN	4.1:1	36
8	$Ph_3PAuCl/AgNO_2$, MeCN	1.9:1	44
9	$IMesAuNTf_2$, MeCN	3.6:1	29
10	$AuCl_3/3AgNTf_2$, MeCN	4.7:1	46
11	$AuCl/AgNTf_2$, MeCN	3.1:1	33
12	$AuCl_3$, MeCN	1:1.6	8
13	$Ph_3PAuNTf_2$, MeCN, 40 °C	6.1:1	79
14	$Ph_3PAuNTf_2$, MeCN, no base	1.2:1	48
15	$Ph_3PAuNTf_2$, MeCN/H_2O = 20:1, no base	[d]	trace
16	$AgNTf_2$, MeCN	1.5:1	22
17	$PdCl_2$, MeCN	1.1:1	8
18	$FeCl_3$, MeCN	2.5:1	9
19	CuI, MeCN	1.6:1	15
20	no catalyst, MeCN	[e]	[e]

[a] Reaction conditions: **1a** (0.2 mmol), Selectfluor (2 equiv), $NaHCO_3$ (2 equiv), catalyst (2.5 mol %), solvent (2 mL), rt, 2.0 h. [b] Determined by GC. [c] Isolated yields. [d] Only **2′a** was isolated in 72% yield. [e] Both **2a** and **2′a** were not detected.

For the initial attempt, 1-phenyl-2-(4-phenylbut-3-yn-2-ylidene)hydrazine **1a** was chosen as a model substrate to optimize the suitable conditions for this fluorinating reaction (Table 1). When the reaction was carried out in the presence of AuCl (2.5 mol % base on **1a**), Selectfluor (2 equiv), and $NaHCO_3$ (2 equiv) in MeCN at room

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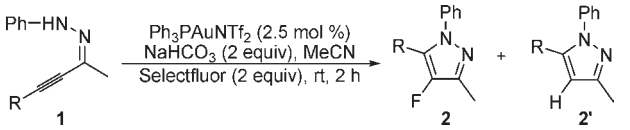
temperature for 2 h, the desired fluorinated pyrazole **2a** was obtained in only 12% yield with low chemoselectivity (entry 1). When Ph_3PAuCl was used as a catalyst, the reaction afforded **2a** in 76% yield (entry 2). Satisfyingly, the yield of **2a** was increased to 81% by using $Ph_3PAuNTf_2$ as a precatalyst under the same reaction conditions (entry 3). Gold precatalyst derived from the combination of AgOTf, $AgSbF_6$, AgF, AgCN, or $AgNO_2$ with Ph_3PAuCl showed a modest catalytic activity (entries 4−8). An NHC ligand-bearing gold(I) complex also showed poor performance in the reaction (entry 9). Besides, gold(III) catalysts presented poor results for the reaction (entries 10 and 12). Solvent has a great effect on the catalytic activity of gold and chemoselectivity of the reaction (see Supporting Information, Table S2). MeCN has proven to be the best choice for the reaction among several solvents screened so far (MeCN, MeCN/H_2O (20/1, v/v), DCE, dioxane, THF, EtOH, pyridine, and DMF). When using MeCN/H_2O (20/1, v/v) as the medium and without addition of a base, only nonfluorinated pyrazole **2′a** was obtained in 72% yield, suggesting that the competitive selectivity between **2a** and **2′a** could be controlled (entry 15 vs entry 3). The yield of **2a** and the chemoselectivity were substantially reduced in the absence of $NaHCO_3$, indicating that the addition of a base was essential for the reaction (entry 14; also see the Supporting Information, Table S1). Control experiments revealed that the tandem cyclization/fluorination did not take place at all without a gold catalyst (entry 20). It was found that other transition metal catalysts such as $AgNTf_2$, $PdCl_2$, $FeCl_3$, or CuI were far less effective than $Ph_3PAuNTf_2$ for the reaction (entries 16−20).

Table 2. Gold-Catalyzed Aminofluorination Reaction of Various Alkynyl Phenylhydrazones **1**[a]

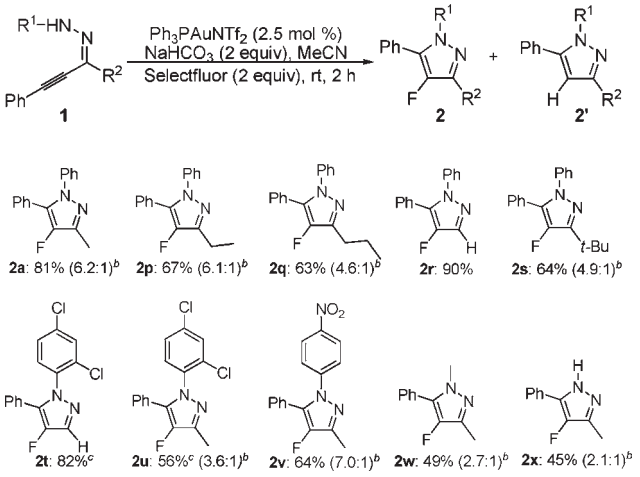


entry	substrate (**1**), R	**2**/**2′**[b]	yield (%, **2**)[c]
1	4-MeC_6H_4 (**1b**)	7.2:1	**2b**, 85
2	4-$MeOC_6H_4$ (**1c**)	5.6:1	**2c**, 81[d]
3	2-$MeOC_6H_4$ (**1d**)	6.3:1	**2d**, 83[e]
4	4-$EtOC_6H_4$ (**1e**)	5.0:1	**2e**, 80
5	4-EtC_6H_4 (**1f**)	4.0:1	**2f**, 73
6	4-(n-C_5H_{11})C_6H_4 (**1g**)	3.8:1	**2g**, 75
7	4-ClC_6H_4 (**1h**)	2.8:1	**2h**, 64
8	3-ClC_6H_4 (**1i**)	4.5:1	**2i**, 73
9	4-BrC_6H_4 (**1j**)	3.3:1	**2j**, 69
10	2-thiophenyl (**1k**)	8.3:1	**2k**, 87
11	n-Bu (**1l**)	4.5:1	**2l**, 78
12	Bn (**1m**)	3.8:1	**2m**, 74[d]
13	t-Bu (**1n**)	5.1:1	**2n**, 75
14	TMS (**1o**)	2.1:1	**2o**, 43

[a] Reaction conditions: **1** (0.2 mmol), Selectfluor (2 equiv), $NaHCO_3$ (2 equiv), $Ph_3PAuNTf_2$ (2.5 mol %), MeCN (2 mL), rt, 2.0 h. [b] Determined by GC. [c] Isolated yields. [d] Na_2CO_3 as the base. [e] NH_4HCO_3 as the base.

With optimized reaction conditions in hand, we then set out to explore the scope of the substrates. First, the scope of alkyne moieties was investigated (Table 2). A variety of alkynyl phenylhydrazones **1** underwent cyclization/fluorination smoothly, displaying a broad substrate compatibility and substituent tolerance (entries 1−14). It was found that electron-rich aryl-bearing alkynyl phenylhydrazones underwent the reaction very well and furnished the corresponding products **2** in moderate to good yields (73−86%, entries 1−6), while those electron-poor aryl-substituted substrates afforded slightly lower yields of products (64−73%, entries 7−9). Aliphatic alkynyl substrates also worked well (entries 11−13). Besides, a satisfying yield of **2k** was obtained in the reaction of a heterocycle-substituted alkynyl substrate **1k** (entry 10). It is noteworthy that the TMS group could be tolerated under the reaction conditions (entry 14).

Scheme 1. Gold-Catalyzed Aminofluorination of Alkynes: The Effect of Substituents on the Hydrazone Moiety[a]



[a] Reaction conditions: **1** (0.2 mmol), Selectfluor (2 equiv), $NaHCO_3$ (2 equiv), $Ph_3PAuNTf_2$ (2.5 mol %), MeCN (2 mL), rt, 2.0 h. [b] The ratio between **2** and **2′** was determined by GC. [c] Reaction temperature at 40 °C.

Next, the substitution variation of the hydrazone moiety was surveyed (Scheme 1). When changing the R^2 group while keeping the phenylhydrazine moiety intact, we found that substrates with longer chain of R^2 gave lower yield of the target product (**2q** vs **2a** vs **2p** vs **2r**). It is noteworthy that the fluoropyrazole was obtained as the sole product

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when R^2 was a hydrogen (**2r**, **2t**). Several other hydrazine units such as 2,4-dichlorophenylhydrazine, 4-nitrophenylhydrazine, methylhydrazine, and hydrazine were surveyed, and in most cases, acceptable yields of products were obtained (45−82%, **2t**−**x**).

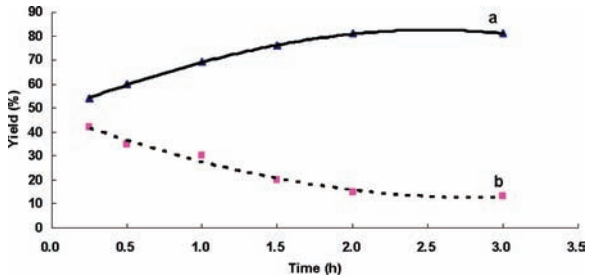
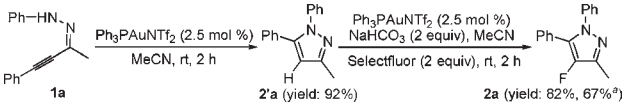


Figure 1. Plots of the yields of **2a** and **2′a** against reaction time (h) for the gold-catalyzed aminofluorination of **1a**. Curves a and b represent the change in the yields of **2a** and **2′a** with the reaction time, respectively.

To gain insight into the mechanism of the reaction, we investigated the change situation of the yields of **2a** and **2′a** during the gold-catalyzed aminofluorination of **1a**. The plots of the yields of **2a** and **2′a** against the reaction time are shown in Figure 1. The results demonstrated that the starting material **1a** was completely consumed within 15 min to give **2a** and **2′a** in a total yield of 96% with a ratio of 54:42 (**2a**/**2′a**). Then **2′a** was gradually converted into **2a** with the proceeding of the reaction, and the final yield of **2a** could reach as high as 81%. The sum of the yields of **2a** and **2′a** remained around 96% over the reaction time, suggesting no formation of other products. In addition, when the preparative protonic product **2′a**, produced from the cyclization of **1a** catalyzed by $Ph_3PAuNTf_2$ (2.5 mol %), was allowed to react with Selectfluor in the presence or absence of a gold catalyst, the desired fluorinated product **2a** could also be obtained in moderate yields (Scheme 2).

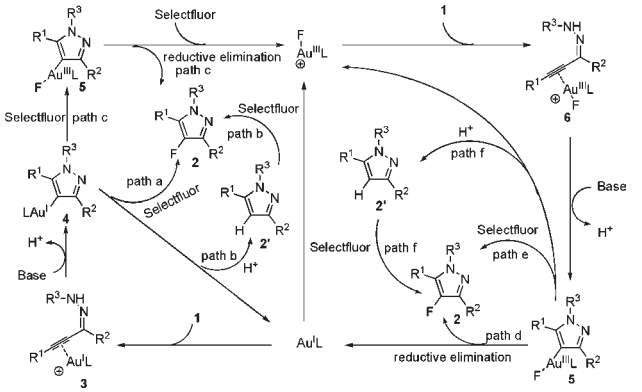
Scheme 2. Synthesis of **2′a** via Gold(I)-Catalyzed Cyclization of **1a** and Its Subsequent Conversion to **2a** in the Presence of Selectfluor[a]



[a] Reaction without a gold catalyst.

On the basis of the aforementioned results and previous literature,[6] several mechanistic manifolds regarding the gold-catalyzed aminofluorination of **1** are depicted in Scheme 3. First, the reaction may proceed via a gold(I) catalytic cycle. Thus, aminoauration of **1** gave intermediate **3**,[11c] subsequent electrophilic fluorodeauration or protodeauration of the vinylgold species **3** leading to the formation of **2** (path a) or **2′**.[6d] Then **2′** was transformed to **2** in the presence of Selectfluor (path b).[2a,b] Since the gold(I) complex could be oxidized into the gold(III) complex in the presence of Selectfluor[9c,e,6] and the gold(III) complex could also catalyze the reaction (Table 1, entry 10), we proposed that those mechanistic pathways involving a redox Au(I)/Au(III) catalytic cycle[6,8,9] were also possible (paths c−f).

Scheme 3. Proposed Mechanism



In summary, we have developed a mild and efficient protocol to access fluoropyrazoles for the first time based on ubiquitous alkyne moieties as backbones involving a gold-catalyzed tandem aminofluorination of alkynes in the presence of Selectfluor. The present method has advantages of mild reaction conditions, high yields, broad substrate scope, and a simple one-pot procedure.

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Supporting Information Available. Experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.