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Gold(I)-Catalyzed Aminohalogenation of Fluorinated *N*′-Aryl-*N*-Propargyl Amidines for the Synthesis of Imidazole Derivatives under Mild Conditions

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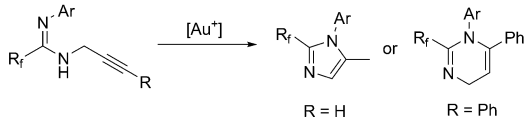
Abstract: A procedure for the synthesis of fluorinated imidazole derivatives from propargyl amidines has been developed. Under gold(I) catalysis, propargyl amidines were converted into 5-fluoromethyl imidazoles in the presence of Selectfluor through a cascade cyclization/fluorination process. In contrast, imidazole-5-carbaldehydes were obtained in high yields when *N*-iodosuccinimide (NIS) was used as the halogenating reagent. The polarity of the solvent and light had significant impact on the formation of the carbaldehydes. These transformations showed excellent functional-group tolerance. An unfluorinated substrate with an electron-withdrawing group also underwent aminohalogenation to give the corresponding product in good yield. Mechanistic investigation revealed the general pathways of these transformations.

Keywords: aminohalogenation · cyclization · gold · homogeneous catalysis · imidazoles

Introduction

The physiochemical properties of organic compounds that contain fluorinated substituents often exhibit significant differences compared to those without such substituents.[1,2] Recently, imidazoles that feature fluorine-containing functional groups have attracted much attention owing to their interesting behavior as pharmaceuticals and agrochemicals.[3] However, the introduction of fluorinated groups into organic molecules represents a major challenge because such methods for the preparation of complex fluorinated compounds are often based on fluorinated building blocks.[4,5,6]

Homogeneous gold catalysis has made significant progress in the last decade. Most of the processes that use gold catalysis rely on the π-acidic nature of the cationic gold species to activate alkynes or alkenes towards nucleophilic addition.[7,8] Following this line of research, in 2007, Sadighi and co-workers reported the direct gold-catalyzed hydrofluorination of alkynes with $Et_3N{\cdot}3HF$ as the nucleophilic fluorine source.[9] In the following year, Gouverneur and co-workers developed an alternative procedure for the gold-catalyzed fluorination of alkynes by using an electrophilic source of fluorine, Selectfluor.[10] Based on this strategy, Gouverneur and co-workers[11a] and de Haro and Nevado[11b,e] independently reported the preparation of α-fluoroenones from propargyl acetates through a gold-catalyzed rearrangement/fluorination cascade, whilst Xu and co-workers[11c,d] applied the gold-catalyzed aminofluorination of alkynes to synthesize fluorinated pyrazoles. These studies have laid the foundation for efficient C_{sp2}–F bond formation by using a Au^I/Au^{III} cycle.[12] Hashmi et al. reported a synthetic route to alkylidenoxazolines and -oxazoles through a gold-catalyzed intramolecular hydroamination of alkynes.[13] Our group has demonstrated that propargyl amidines could be converted into imidazoles by gold-catalyzed *5-exo-dig* cyclization (Scheme 1).[14] In these reactions, vinyl–gold species[15] were



Scheme 1. Gold(I)-catalyzed aminohydrogenation.

proposed as the intermediates that effectively underwent C_{sp2}–X bonds formation.[10,12a,16] Herein, we report our work on the gold-catalyzed aminofluorination reaction to give 5-fluoromethyl imidazoles through a cyclization/fluorination cascade process that involves the construction of new C_{sp3}–F bonds. Similarly, the analogous aminoiodination afforded 5-iodomethyl imidazoles, which were converted into imidazole-5-carbaldehydes in air.

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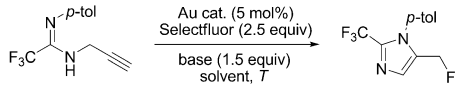
Results and Discussion

We selected 2-trifluoromethyl-*N*-*p*-tolyl-*N*-propargyl amidine (**1b**) as the model substrate to optimize the reaction conditions. Preliminary studies showed that both the catalyst and the base played important roles in the reaction: Propargyl amidine **1b** decomposed on treatment with Selectfluor in the absence of catalyst or base (Table 1, entries 1 and 2). When the reaction was carried out in the presence of [Ph_3PAuCl] (5 mol%), Selectfluor (2.5 equiv), and $NaHCO_3$ (1.5 equiv) in CH_3CN at 80 °C for 2 h, 5-fluoromethyl imidazole **2b** was observed as the sole product in 55% yield (Table 1, entry 3). Optimization studies were carried out to determine the best general conditions. CH_3CN and Na_2CO_3 were identified as the best solvent and base for this transformation, respectively, and compound **2b** was obtained in 82% yield when the reaction was carried out at 60 °C (Table 1, entry 10). When a halogenated solvent was used in place of CH_3CN, only the protonated product was obtained, owing to the decomposing of Selectfluor (Table 1, entries 13 and 14). [IPrAuCl] was less efficient for this transformation compared to [Ph_3PAuCl] (Table 1, entries 17 and 18). None of the desired product was detected when *N*-fluorobenzenesulfonimide (NFSI), another electrophilic fluorinating reagent, was used (Table 1, entry 19).

Table 1. Optimization of the aminofluorination of *N*-tolyl propargyl amidine **1b**.

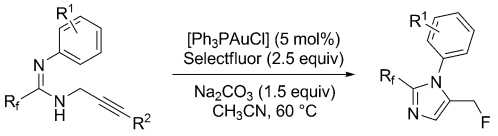


1b **2b**

Entry	Catalyst	Base	Solvent	*T* [°C]	Yield [%][a]
1	–	$NaHCO_3$	CH_3CN	80	–
2	[Ph_3PAuCl]	–	CH_3CN	80	–
3	[Ph_3PAuCl]	$NaHCO_3$	CH_3CN	80	55
4	[Ph_3PAuCl]	$NaHCO_3$	CH_3CN	100	32
5	[Ph_3PAuCl]	$NaHCO_3$	CH_3CN	60	53
6	[Ph_3PAuCl]	$NaHCO_3$	CH_3CN	45	41
7	[Ph_3PAuCl]	CH_3COOK	CH_3CN	80	30
8	[Ph_3PAuCl]	K_2CO_3	CH_3CN	80	15
9	[Ph_3PAuCl]	Na_2CO_3	CH_3CN	80	73
10	[Ph_3PAuCl]	Na_2CO_3	CH_3CN	60	82
11	[Ph_3PAuCl]	Na_2CO_3	DMF	80	–
12	[Ph_3PAuCl]	Na_2CO_3	toluene	80	–
13	[Ph_3PAuCl]	Na_2CO_3	CH_2Cl_2	RT	87[b]
14	[Ph_3PAuCl]	Na_2CO_3	DCE	80	75[b]
15	[Ph_3PAuCl]	Na_2CO_3	THF	60	–
16	[Ph_3PAuCl]	Na_2CO_3	acetone	60	40
17	[IPrAuCl]	Na_2CO_3	acetone	60	70
18	[IPrAuCl]	Na_2CO_3	CH_3CN	60	59
19	[Ph_3PAuCl]	Na_2CO_3	CH_3CN	60	–[c]

[a] Yield of isolated product. [b] The product was 2-trifluoromethyl-5-methyl imidazole. [c] NFSI was used as the fluorinating reagent. *p*-tol = *p*-toluene, DCE = 1,2-dichloroethane.

Table 2. Gold(I)-catalyzed aminofluorination of fluorinated propargyl amidines.



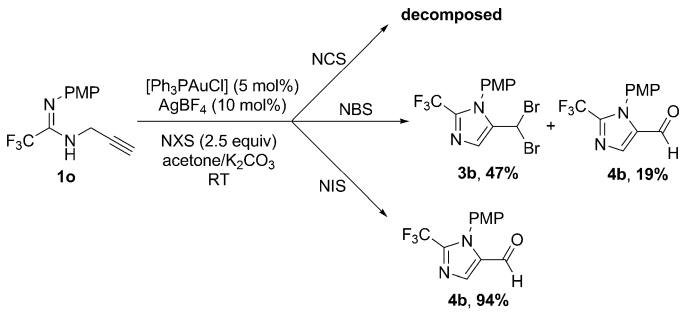
1 **2**

Entry	R_f	R^1	R^2	**2**	Yield [%][a]
1	CF_3	H	H	**2a**	78
2	CF_3	*p*-CH_3	H	**2b**	82
3	CF_3	*m*-CH_3	H	**2c**	77
4	CF_3	*m*-Cl	H	**2d**	70
5	CF_3	*p*-I	H	**2e**	74
6	CF_3	*p*-COOEt	H	**2f**	71
7	CF_3	*P*-NO_2	H	**2g**	60
8	CF_3	*p*-CN	H	**2h**	68
9	CF_3	*p*-CF_3	H	**2i**	55
10	CF_3	naphthyl	H	**2j**	49
11	CF_3	*o*-Ph	H	**2k**	31
12	CF_3	*o*-OCH_3	H	**2l**	42
13	CF_3	*o*-F	H	**2m**	57
14	CF_3	*p*-OCH_3	Ph	–	–
15	CF_2Br	*p*-OCH_3	H	–	–
16	CF_2H	H	H	**2n**	65

[a] Yield of isolated product.

With the optimized conditions in hand, we proceeded to investigate the scope of this transformation. As summarized in Table 2, our results showed broad functional-group compatibility: Propargyl amidines with substituents at the *para* or *meta* positions of the phenyl ring all gave good yields of their corresponding products (Table 2, entries 2, 3, and 5). Propargyl amidines with strongly electron-withdrawing groups gave lower yields (Table 2, entries 7–9) and steric hindrance was also found to have a significant influence on the yield of the products. *N*-naphthyl propargyl amidine **1j** or substrates that contained a substituent at the *ortho* position of the phenyl ring afforded very low yields (Table 2, entries 10–13). A substrate with a phenyl group on the alkyne terminus was not suitable in this transformation (Table 2, entry 14). The effect of fluoroalkyl groups was also examined. Propargyl amidines with a CF_3 group effectively underwent cyclization/fluorination to give the product in moderate-to-good yield. However, no product was obtained when a substrate with a CF_2Br group was used, presumably owing to its poor stability (Table 2 entry 15). On the contrary, a substrate with a CF_2H group reacted smoothly to give the desired product in moderate yield (Table 2, entry 16).

Next, we investigated the reaction of fluorinated *N*-propargyl amidines with other electrophilic halogenating reagents.[10,17] Unfortunately, the chloroamination of *N*-propargyl amidine **1o** in the presence of cationic gold(I) and *N*-chlorosuccinimide (NCS) in acetone was unsuccessful. With *N*-bromosuccinimide (NBS) as the halogenating reagent, 5,5-dibromomethyl imidazole **3b** was obtained in 47% yield under the same conditions, whilst a byproduct, imidazole-5-carbaldehyde **4b**, was also isolated in 19% yield (see Scheme 2). Surprisingly, imidazole-5-carbaldehyde **4b** was formed as the sole product in excellent yield (94%) when *N*-propargyl amidine was treated with NIS (Scheme 2). This product is most likely formed from 5-monohalomethyl imid-



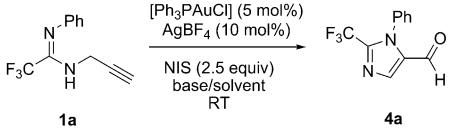
Scheme 2. Reaction of fluorinated propargyl amidine **1o** with electrophilic reagents such as NCS, NBS, or NIS.

azole through halogen-atom elimination. The elimination of bromine is more difficult than iodine. Meanwhile, the increased acidity of the hydrogen atom in the bromomethyl group, owing to the presence of the electron-withdrawing CF_3 group, led to the formation of 5,5-dibromomethyl imidazole **3b** through a haloform reaction under basic conditions. Control experiments indicate that 5,5-dibromomethyl imidazole **3b** is stable at room temperature and does not undergo hydrolysis.

Studies were undertaken to identify general reaction conditions in the presence of NIS. The reaction of the gold precursor with a Ag salt formed the cationic gold(I) catalyst. Base was desirable to promote the formation of the carbaldehyde; K_2CO_3 appeared to be particularly suitable and an excellent yield of 98% was obtained when 1.0 equivalent of K_2CO_3 was added (Table 3, entries 1 and 2). Lowering the amount of NIS resulted in a lower yield of the product (Table 3, entry 3). Solvent was essential for this transformation. A higher yield was obtained when the reactions were carried out in polar solvents, except for water, owing to the poor solubility of NIS in water. Acetone was the best solvent for this reaction (Table 3, entries 2, 4–7). Control experiments revealed that this transformation could take place without a gold(I) catalyst, but in very low yield. Raising the temperature of the reaction improved the yield of the imidazole-5-carbaldehyde (Table 3, entries 12 and 13).

With the standard reaction conditions in hand, we set out to explore the scope of the propargyl amidines. Unlike aminofluorination, neither the electronic properties nor the steric bulk of the substituents on the phenyl ring had much impact on the transformations (Table 4, entries 2 versus 7 and entries 1 versus 8). Lower yields were obtained for substrates that contained a CF_2Br substituent, presumably owing to their instability under the reaction conditions (Table 4, entries 10–12). Moreover, imidazole-5-carbaldehydes were obtained as the sole products from substrates with a terminal alkyne group. A substrate that contained a Ph group at the propargylic position could be converted into 5-iodo-1,4-dihydropyrimidine in moderate yield, but the product was very instable, even at low temperatures (Table 4, entry 9). Gratifyingly, unfluorinated propargyl amidine also reacted effectively to give the corresponding product in good yield (Table 4, entry 15).

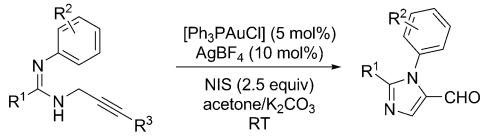
Table 3. Optimization of the synthesis of imidazole-5-carbaldehyde **4a**.



Entry	Catalyst	Base	Solvent	Yield [%][a]
1	$[Ph_3PAuCl]/AgBF_4$	–	acetone	65
2	$[Ph_3PAuCl]/AgBF_4$	K_2CO_3	acetone	98
3	$[Ph_3PAuCl]/AgBF_4$	K_2CO_3	acetone	46[b]
4	$[Ph_3PAuCl]/AgBF_4$	K_2CO_3	water	50
5	$[Ph_3PAuCl]/AgBF_4$	K_2CO_3	CH_3CN	76
6	$[Ph_3PAuCl]/AgBF_4$	K_2CO_3	CH_2Cl_2	58
7	$[Ph_3PAuCl]/AgBF_4$	K_2CO_3	toluene	42
8	$[Ph_3PAuCl]/AgBF_4$	Na_2CO_3	acetone	77
9	$[Ph_3PAuCl]/AgBF_4$	Et_3N	acetone	70
10	$[Ph_3PAuCl]/AgSbF_6$	K_2CO_3	acetone	75
11	$[Ph_3PAuCl]/AgClO_4$	K_2CO_3	acetone	50
12	–	K_2CO_3	acetone	47
13	–	K_2CO_3	acetone	30[c]

[a] Yield of isolated product. [b] NIS (1.0 equiv). [c] 60 °C.

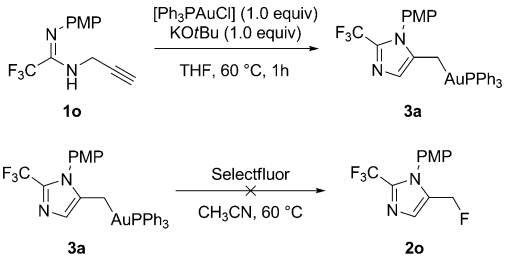
Table 4. Gold(I)-catalyzed synthesis of imidazole-5-carbaldehydes.



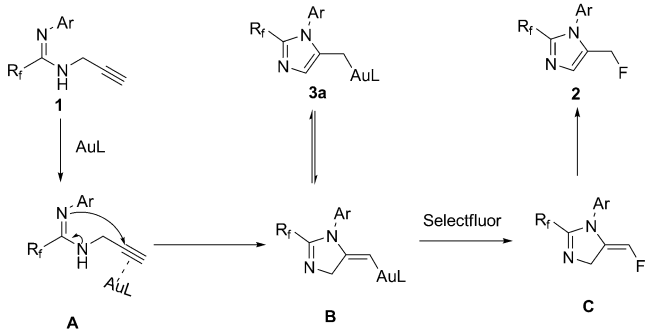
Entry	R^1	R^2	R^3	**4**	Yield [%][a]
1	CF_3	H	H	**4a**	98
2	CF_3	*p*-OCH_3	H	**4b**	94
3	CF_3	*p*-Cl	H	**4c**	82
4	CF_3	*m*-CF_3	H	**4d**	91
5	CF_3	*o*-CH_3	H	**4e**	89
6	CF_3	*o*-I	H	**4f**	87
7	CF_3	*p*-CO_2Et	H	**4g**	95
8	CF_3	*o*-Ph	H	**4h**	90
9	CF_3	*p*-OCH_3	Ph	**4i**[b]	74
10	CF_2Br	*p*-CH_3	H	**4j**	69
11	CF_2Br	*p*-CN	H	**4k**	57
12	CF_2Br	*o*-Br	H	**4l**	46
13	CF_2H	H	H	**4m**	81
14	CF_2CF_3	H	H	**4n**	93
15	CO_2Et	H	H	**4o**	86

[a] Yield of isolated product. [b] The product was 5-iodo-1,4-dihydropyrimidine.

To investigate the mechanism of the aminofluorination reaction, a gold(I)–alkyl species (**3a**) was prepared by the reaction of $[Ph_3PAuCl]$ with KO*t*Bu. However, no monofluorinated product was obtained from the treatment of compound **3a** with Selectfluor (Scheme 3). This result suggests that the monofluorinated product is most likely formed directly from vinyl–gold species. The proposed mechanism is shown in Scheme 4. First, the propargyl amidine interacts with the gold center to form a π complex (**A**). This intermediate undergoes nucleophilic attack in a *5-exo-dig* mode to form the vinyl–gold species (**B**), which has a tautomerism



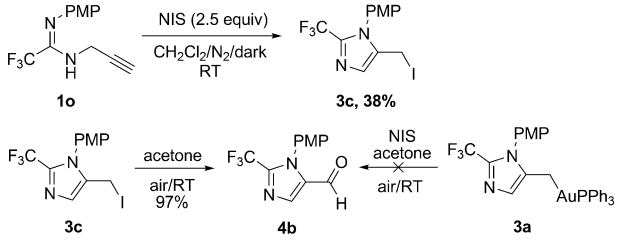
Scheme 3. Substrates for the mechanism investigation.



Scheme 4. Proposed mechanism for the gold(I)-catalyzed aminofluorination reaction.

equilibrium with imidazole–gold species **3a**. Then, vinyl–gold intermediate **B** reacts with Selectfluor to generate the vinyl–fluoride product (**C**), which is aromatized to afford the final product (**2**).

These aforementioned control experiments demonstrated that the formation of imidazole-5-carbaldehydes could take place without a gold(I) catalyst, although the yield was very low. With CH_2Cl_2 as the solvent, 5-iodomethyl imidazole **3c** was prepared in 38% yield in the absence of a catalyst under a N_2 atmosphere (Scheme 5).[17e,18] We also found that

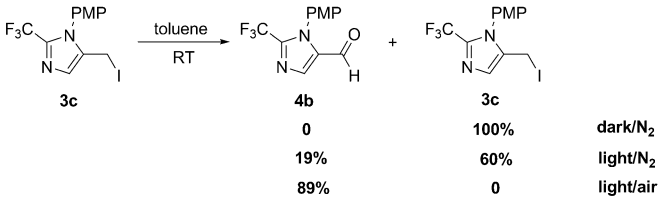


Scheme 5. Reactions without a gold(I) catalyst.

5-iodomethyl imidazole could be efficiently converted into imidazole-5-carbaldehyde **4b** in air. However, the treatment of compound **3a** with NIS showed no formation of compound **4b**, but, instead, resulted in the decomposition of compound **3a** (Scheme 5). Based on these observations, we inferred that imidazole-5-carbaldehyde **4b** originated directly from 5-iodomethyl imidazole **3c** and that this process did not involve the gold(I) catalyst.

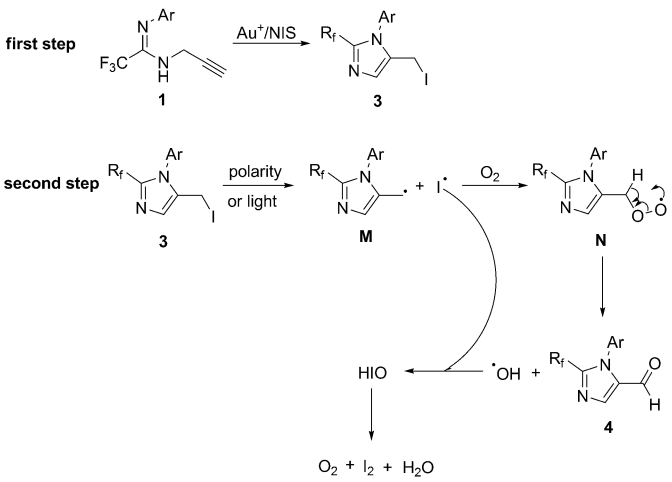
Naturally, the carbonyl oxygen atom was supposed to be taken from air. Under a N_2 atmosphere and in darkness, 5-iodomethyl imidazole **3c** could be stored for a long time in non-polar solvent. When it was exposed to dry air, 5-iodomethyl imidazole **3c** was gradually converted into imidazole-5-carbaldehyde **4b**. However, compound **3c** was stable in water. These results indicated that the carbonyl oxygen atom was most likely obtained from air.

Further study indicated that light had a significant impact on the formation of imidazole-5-carbaldehydes when the reaction was performed in non-polar solvent. As noted above, 5-iodomethyl imidazole **3c** could be stored for a long time when the system was kept in the dark under a N_2 atmosphere. However, in the presence of air and light, 5-iodomethyl imidazole **3c** was quickly converted into imidazole-5-carbaldehyde. In this experiment, the color of the solution gradually turned red, owing to the generation of iodine. When exposed to light under a N_2 atmosphere, only a 19% yield of carbaldehyde **4b** was detected. It is possible the residual O_2 in the N_2 gas reacted with compound **3c** to form compound **4b** (Scheme 6).



Scheme 6. Effect of light on the formation of imidazole-5-carbaldehydes.

Our proposed pathway for the formation of imidazole-5-carbaldehydes is shown in Scheme 7. Catalyzed by the cationic Au^I species, propargyl amidine **1** is converted into 5-iodomethyl imidazole, as in the formation of 5-fluoromethyl imidazole (Scheme 4). A radical intermediate (**M**) and an iodine radical are created by homolytic cleavage of the C–I



Scheme 7. Proposed mechanism for the formation of imidazole-5-carbaldehydes.

bond.[19] The polarity of the solvent and light are both essential for the formation of these radical intermediates. Species **M** then combines with O_2 to give a peroxy-radical species (**N**).[20] In a concerted reaction, species **N** releases a hydroxyl radical to afford carbaldehyde **4**. I_2 is most likely generated through the decomposition of HIO, which was formed from the combination of iodine radicals with hydroxyl radicals.

Conclusion

In conclusion, we have presented a simple, mild, and efficient method for the preparation of 2-fluoroalkyl-imidazole derivatives from fluorinated propargyl amidines. Under gold(I) catalysis, fluorinated propargyl amidines underwent a *5-exo-dig*-cyclization/fluorination cascade reaction in the presence of Selectfluor with the construction of new C_{sp3}–F bonds. Treatment with NIS afforded the conversion of fluorinated and unfluorinated propargyl amidines into imidazole-5-carbaldehydes in good-to-excellent yields. Our mechanistic investigation revealed that both transformations involved a vinyl–gold intermediate (**B**; Scheme 4), which underwent halogenation to form 5-halogenmethyl imidazole. 5-Iodomethyl imidazoles were converted into imidazole-5-carbaldehydes through a radical mechanism.

Acknowledgements

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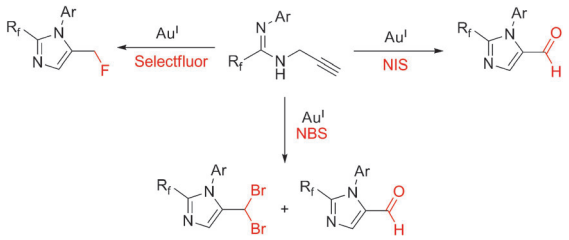

Golden(I): Under gold(I) catalysis, propargyl amidines were converted into 5-fluoromethyl imidazoles in the presence of Selectfluor. Treatment with *N*-iodosuccinimide afforded imidazole-5-carbaldehydes as the final product (see scheme).

Gold(I) Catalysis

*S. Li, Z. Li, Y. Yuan, Y. Li, L. Zhang, Y. Wu** ..... ▮▮▮▮–▮▮▮▮

Gold(I)-Catalyzed Aminohalogenation of Fluorinated *N*′-Aryl-*N*-Propargyl Amidines for the Synthesis of Imidazole Derivatives under Mild Conditions