ORGANIC LETTERS

2013
Vol. 15, No. 24
6210–6213

One-Pot Synthesis of 1-(Trifluoromethyl)-4-fluoro-1,2-dihydroisoquinolines and 4,4-Difluoro-1,2,3,4-tetrahydroisoquinolines

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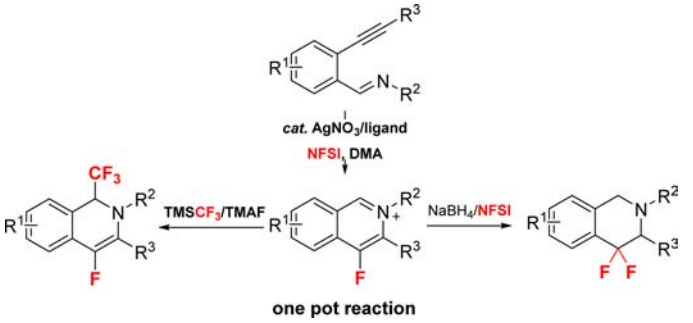
Received October 24, 2013

ABSTRACT



A cascade approach to 1-(trifluoromethyl)-4-fluoro-1,2-dihydroisoquinolines and 4,4-difluorotetrahydroisoquinolines has been developed. The procedure involves a silver-catalyzed intramolecular aminofluorination of alkyne. This one-pot reaction provides an efficient way to synthesize various fluorinated isoquinolines.

As one of the most universal skeletons, nitrogen-containing heterocycles are found in many bioactive chemicals as well as drug molecules.[1] Despite the significant fluorine effect that is conferred by fluorine on physiochemical properties of various drug candidates and materials,[2] introduction of fluorine or fluorine-containing functional groups into heterocycles still seriously lags behind social needs.[3] Thus, enriching the library of fluorine containing heterocycles is an urgent task for chemists and will be beneficial for medicinal and material sciences.[4]

Fluorinated isoquinolines derivatives are prevalent in bioactive compounds and drug candidates.[5−7] For example, 4-fluoro-2*H*-isoquinolin-1-one derivatives have been tested to be a tumor necrosis factor[5] and FMIQ a plasma

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10.1021/ol403059z
Published on Web 11/21/2013

substitute.[6] 4,4-Difluorotetrahydroisoquinoline derivatives showed excellent inhibitory activity against TRPM8 (transient receptor potential melastatin 8)[7] and voltage-gated sodium ion channel[8] (Figure 1).

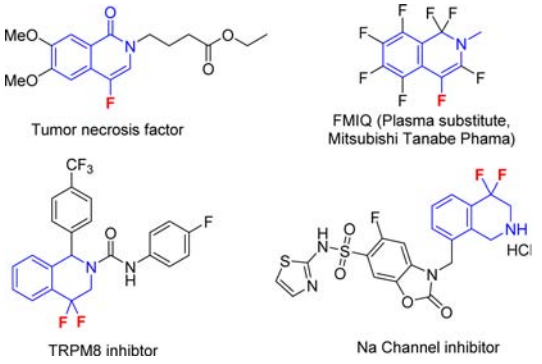
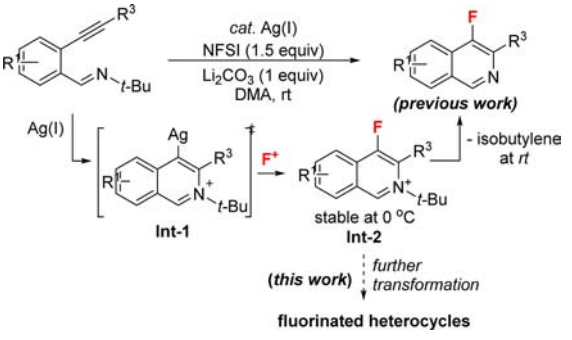


Figure 1. Some prevalent bioactive fluorinated isoquinoline derivatives.

However, access to 4-fluoroisoquinoline derivatives generally requires a strong base, such as ^{n}BuLi, to generate a nucleophilic carbanion to attack the F^+ reagent which suffers from a poor functional group compatibility.[9] Traditional synthesis of *gem*-difluorinated (CF_2) heterocycles usually adopt nucleophilic fluorination of carbonyl group with diethylaminosulfur trifluoride (DAST),[10] or double electrophilic fluorination of carbonyl compounds with F^+ reagent.[7] Similarly, these reactions exhibited limited substrate scopes. In addition, simultaneously introducing fluorine and fluorine-containing group into one molecular is even more challenging.

Scheme 1. Silver-Catalyzed Aminofluorination of Alkynes and Related Transformations



Transition-metal-mediated or -catalyzed fluorinations have been proven to be efficient strategies to introduce fluorine into organic compounds.[11] As part of our ongoing program on transition-metal-catalyzed fluorination reactions,[12] we recently reported a silver-catalyzed aminofluorination of alkynes to achieve fluorinated isoquinolines (Scheme 1).[13] Further mechanistic studies suggested that fluorinated intermediate isoquinolinium **Int-2**, derived from oxidative fluorination of the sp^2 C−Ag bond of **Int-1** by F^+, is stable at 0 °C. But this intermediate gradually decomposed to isoquinoline by releasing isobutene at room temperature. Inspired by this understanding, we envisioned that further transformation of active isoquinolinium **Int-2** would lead to diverse fluorinated isoquinoline derivatives. Herein, we report a tandem processes for the efficient synthesis of 1-(trifluoromethyl)-4-fluoro-1,2-dihydroisoquionline and 4,4-difluoro-1,2,3, 4-tetrahydroisoquionline in one pot.

Because of the special function of the CF_3 moiety in medicinal chemistry, CF_3^- was employed as a nucleophile to test our above hypothesis by combining Ruppert's reagent ($TMSCF_3$) and fluoride salts.[14,15] To our disappointment, as shown in the Supporting Information, the sequential process of aminofluorination of **1a** and trifluoromethylation could not deliver the desired product **2a** under the previous reaction conditions at room temperature. Instead, 4-fluoroisoquinoine was isolated as a major product, which suggests the decomposition of **Int-2** is prior to nucleophilic attack by CF_3^-. Considering the thermostability of **Int-2** at low temperature, the sequential process was conducted at 0 °C. We were delighted to find that the desired product **2a** was obtained albeit in low yield (15%) in the presence of 20 mol % of Ag catalyst. Further optimization of reaction conditions revealed that the yield could be improved by increasing the amount of silver catalyst. In addition, reduced the amount of NFSI was also beneficial to improve the yield of **2a** but resulted in a significant amount of protonolysis byproduct **2a′** (eq 1).[16] Mechanistic studies revealed that the unsuccessful catalytic aminofluorination was resulted from the generation of inactive $AgN(SO_2Ph)_2$ catalyst at 0 °C.[17] With this process, a variety

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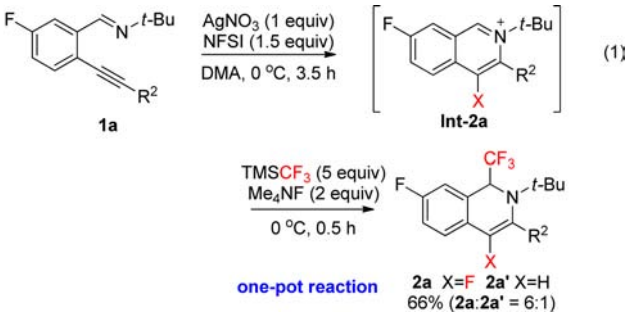
(16) For details, see the Supporting Information.

(17) $AgN(SO_2Ph)_2$, independently synthesized, was proven to be an inactive catalyst for aminofluorination of alkyne at 0 °C but active at room temperature or higher temperature.

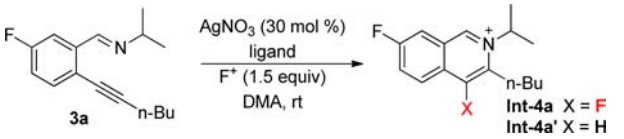
of substrates presented similar chemoselectivity to give a mixture of fluorinated products and protonolysis products, which is difficult to separate to obtain pure product.[18]



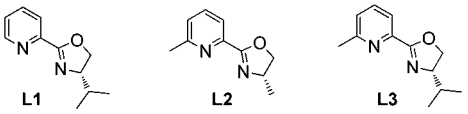
Based on the above results, we turned our attention to address two issues: (1) how to achieve a catalytic reaction and (2) how to suppress the protonolysis product? First, previous data implied that the catalytic reaction could be achieved at room temperature or even higher temperature. We surmised that secondary or primary alkyl-substituted isoquinolinium should be more stable than *tert*-butylisoquinolinium. Thus, substrate **3a** was treated with a catalytic amount of silver catalyst at room temperature. We are delighted to find that the yield of desired product **4a** was increased to 40% ^{19}F NMR yield. However, the reaction also afforded a significant amount of protonated byproduct **4a′** in 18% ^{19}F NMR yield, which possibly derived from the protonolysis of aryl C−Ag bond.[19,20] In order to address this issue, the aminofluorination of **3a** was revisited. As shown in Table 1, the reaction did afford fluorinated isoquinolinium **Int-4a** in 58% yield, combined with isoquinolinium **Int-4a′** in 30% yield. Further optimization process was conducted to reduce the protonolysis product **Int-4a′**. Screening of electrophilic fluorination reagents indicated that SelectFluor gave slightly worse result, but *N*-fluoropyrindinium salts were inactive for aminofluorination. In order to suppress protonation reaction, several nitrogen-based ligands were screened. Commonly used bisnitrogen ligands, such as 1,10-phenanthroline, 2,2′-bipyridine, presented opposite reactivity to give protonated product (entries 6 and 7). Monodentate ligand 2-methylpyridine showed promising efficacy (entry 8). To our delight, 2-oxazolylpyridine ligands, such as **L1**-**L3**, are vital to improve the selective aminofluorination as well as reaction yield. Among them, **L3** gave the best result, even in the presence of 20% silver catalyst (entries 9−12). Those results demonstrated that the coordination of ligand **L3** to silver is helpful to promote oxidative fluorination of C−Ag bond of **Int-1**.

Under optimized catalytic conditions, the substrate scope was investigated (Scheme 2). First, functional groups (R^1), such as F, Cl, and methoxy, were compatible with the

Table 1. Ag-Catalyzed Aminofluorination of Alkynes[a]

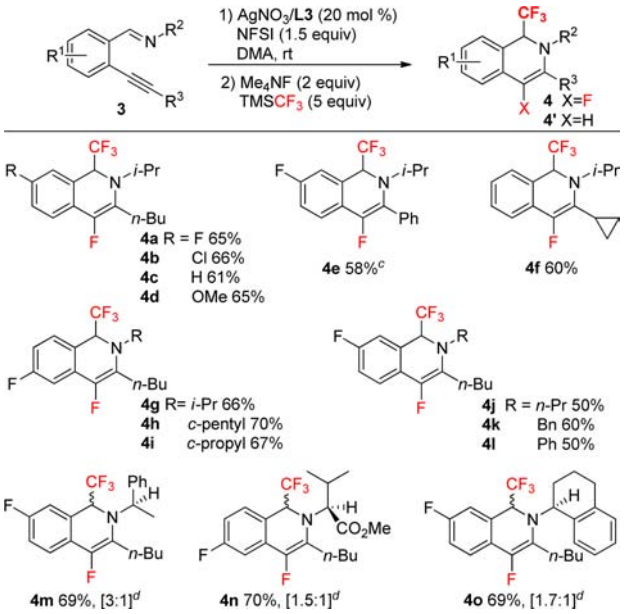


Entry	[F$^+$]	ligand (mol %)	Int-4a/Int-4a' (%)[b]
1	NFSI	--	58/30
2	SelectFluor	--	50/24
3	F-Py-OTf	--	0/90
4	F-2,6-Cl_2Py-OTf	--	0/20
5	F-2,4,6-Me_3Py-OTf	--	0/74
6	NFSI	Phen (30)	5/58
7	NFSI	Bipy (30)	5/54
8	NFSI	2-MePy (30)	72/28
9	NFSI	**L1** (30)	78/18
10	NFSI	**L2** (30)	91/9
11	NFSI	**L3** (30)	96/4
12	NFSI	**L3** (20)[c]	94/6



[a] Reaction conditions: **3a** (0.1 mmol), $AgNO_3$ (30 mol %), F^+ (0.15 mmol), ligand, DMA (1 mL), 3.5 h. [b] FNMR yield with $CF_3CON(CH_3)_2$ as internal standard. [c] $AgNO_3$ (20 mol %).

Scheme 2. Silver-Catalyzed Cascade Aminofluorination of Alkynes and Nucleophilic Addition[a−c]



[a] Reaction conditions: **3** (0.2 mmol), $AgNO_3$ (20 mol %), **L3** (20 mol %), NFSI (0.3 mmol) in DMA (2 mL) at rt for 3.5 h, then Me_4NF (0.4 mmol), $TMSCF_3$ (1 mmol). for 0.5 h; except **4e**, all reactions F/H ratio >10:1. [b] Isolated yield of product **4**. [c] F/H ratio is 3:1. [d] The ratio of diastereoisomers.

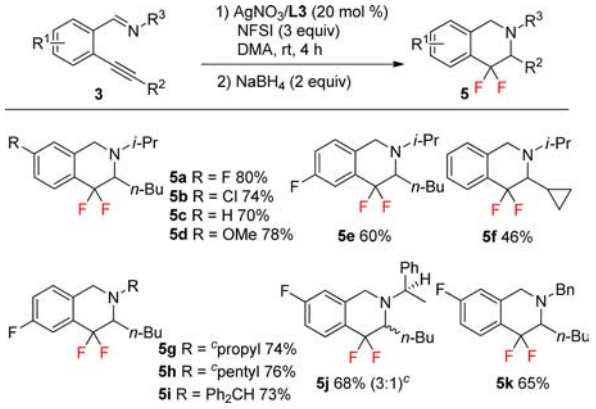
reaction conditions to give products **4a**−**d** in around 60% yields. Second, substrates bearing alkyl, aryl, and cyclopropyl group (R^3) afforded products **4e**,**f** in acceptable

(18) For details, see Table S2 in the Supporting Information.

(19) Increasing the amount of NFSI could suppress protonolysis of aryl C−Ag complex. However, an excess amount of NFSI also suppress the trifluoromethylation step, which results in a poor yield.

(20) A similar observation was reported in Ag-catalyzed fluorination; see: (a) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860–2863. (b) Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662–1663.

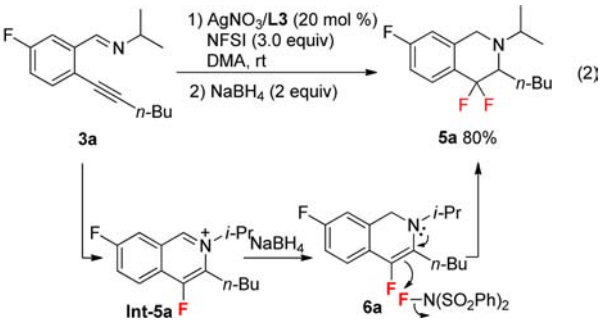
Scheme 3. Cascade Reaction for *gem*-Difluorinated Cyclic Amine[a]



[a] Reaction conditions: **3** (0.2 mmol), NFSI (0.6 mmol), $AgNO_3$ (20 mol %), **L3** (20 mol %) in DMA (2 mL) at rt for 4 h, then $NaBH_4$ (0.4 mmol), 0.5 h. [b] Isolated yield. [c] Diastereoselectivity.

yields. Moreover, different substituents on imine (R^2), such as alkyl and phenyl, did not affect the reaction to give products **4g**–**l** in moderate yields. In order to achieve asymmetric trifluoromethylation, chiral amine was introduced to substrates, such as **3m**–**o**. Unfortunately, although **4m**–**o** were obtained in good yields, poor diastereoselectivities were observed. Notably, all above substrates, except **3e**, could be transformed to related product **4** with excellent F/H ratio (> 10:1). The reaction of **3e** presented a poor F/H selectivity to give a mixture of **4e** and **4e′** with 3:1 ratio.

As we know, the active isoquinolinium intermediate, **Int-5a**, can be easily reduced to give a cyclic enamine. Thus, the fluorinated isoquinolinium generated in situ was treated by $NaBH_4$. Surprisingly, the reaction did not afford the related enamine product **6a**. Instead, 4,4-difluoroterahydroisoquinoline **5a** was isolated in 36% yield. Increasing the amount of NFSI to 3 equiv afforded **5a** in 80% isolated yield. It is possible that **6a** could further react with NFSI via an electrophilic fluorination process to deliver *gem*-difluoro compounds **5a** (eq 2). Due to the important function of *gem*-difluorocyclic amine in medicinal chemistry, further substrate scope was surveyed. As shown in Scheme 3, the reaction exhibited broad substrate scope and delivered a series of 4,4-difluorotetrahydroisoquinolines (**5a**–**k**) in good yields. To the best of our knowledge, this method represents the first example of efficient synthesis of *gem*-difluorinated heterocycles products in a one-pot reaction.



In summary, we have developed a cascade procedure for the synthesis of 1-(trifluoromethyl)-4-fluoro-1,2-dihydroisoquinoline and 4,4-difluoro-1,2,3,4-tetrahydroisoquinoline in a one pot reaction. The reaction enriches the tool box for the synthesis of fluorinated heterocycles which could be applied in medicinal chemistry. Further efforts on the synthesis of more complex molecules and exploration of their biological activities are in progress.

Acknowledgment. We are grateful for financial support from the National Basic Research Program of China (973-2011CB808700), the National Nature Science Foundation of China (Nos. 20923005, 2125210, 21202185, and 21121062), the Science and Technology Commission of the Shanghai Municipality (11JC1415000), and the CAS/SAFEA International Partnership Program for Creative Research Teams.

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

The authors declare no competing financial interest.