ORGANIC LETTERS

2012
Vol. 14, No. 21
5416–5419

Ag(I)-Catalyzed Aminofluorination of Alkynes: Efficient Synthesis of 4-Fluoroisoquinolines and 4-Fluoropyrrolo[α]isoquinolines

Tao Xu and Guosheng Liu*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Lingling Road, Shanghai, 200032, China

gliu@mail.sioc.ac.cn

Received September 8, 2012

ABSTRACT

A silver-catalyzed intramolecular oxidative aminofluorination of alkynes has been developed by using NFSI as a fluorinating reagent. This reaction represents an efficient method for the synthesis of various 4-fluoroisoquinolines and 4-fluoropyrrolo[α]isoquinolines.

The introduction of fluorine into drugs often leads to a significant improvement of their medicinal properties which have resulted in a revolution of the pharmaceutical industry in recent decades.[1] So far, more than 20% of commercial drugs contain fluorine. Heterocycles are often a key core of bioactive molecules. Thus, exploration of a new synthetic strategy for the synthesis of fluorinated heterocycles has attracted attention.[2]

Isoquinolines and pyrrolo[α]isoquinolines represent structure moieties which are extensively presented in biological natural products as well as drug molecules.[3] For example, berberine[3d] is an antitumor compound that shows inhibition of HIV replication, and Lamellarin D[3e,f] is an anticancer alkaloid for inhibition of human topoisomerase I (Figure 1). The oxidation product, such as 4-hydroxyisoquinoline, is the major metabolite of isoquinoline.

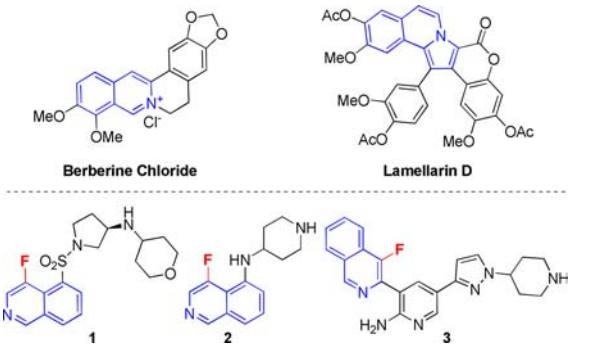


Figure 1. Representive bioactive isoquinoline and pyrrolo[α]-isoquinoline and related fluorinated compounds.

(1) (a) Filler, R.; Kobayashi, Y. In *Biomedicinal Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1982. (b) Welch, J. T.; Eswarakrishman, S., Eds. In *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991.

(2) For some reviews on the synthesis of fluorinated heterocycles, see: (a) Petrov, V. A. In *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry,and Applications*; John Wiley & Sons, Inc.: Hoboken, NJ, 2009. (b) Nosova, E. V.; Lipunova, G. N.; Charushin, V. N.; Chupakhin, O. N. *J. Fluorine Chem.* **2010**, *131*, 1267–1288. (c) Zhu, S.; Wang, Y.; Peng, W.; Song, L.; Jin, G. *Curr. Org. Chem.* **2002**, *6*, 1057–1096. (d) Silvester, M. J. *Aldrichimica Acta* **1991**, *24*, 31–38. For some selective examples, see: (e) Kwiatkowski, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 1738–1741. (f) Kishi, Y.; Nagura, H.; Inagi, S.; Fuchigami, T. *Chem. Commun.* **2008**, 3876–3878. (g) Fustero, S.; Catalan, S.; Sanchez-Rosello, M.; Simon-Fuentes, A.; del Pozo, C. *Org. Lett.* **2010**, *12*, 3484–3487.

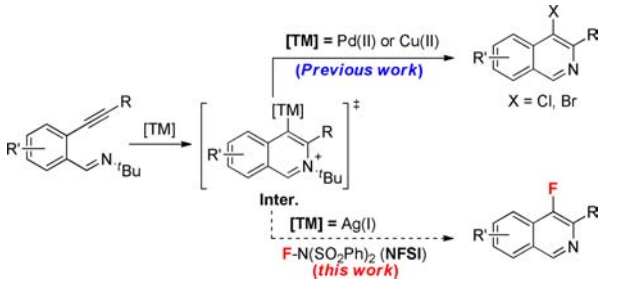
(3) (a) Bentley, K. W. In *The Isoquinoline Alkaloids*; Hardwood Academic: Amsterdam, 1998. (b) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, 2003. (c) Dzierszinski, F.; Coppin, A.; Mortuaire, M.; Dewally, E.; Slomianny, C.; Ameisen, J.-C.; DeBels, F.; Tomavo, S. *Antimicrob. Agents Chemother.* **2002**, *46*, 3197–3207. (d) Kong, L.; Cheng, C.; Tan, R. *Planta Med.* **2001**, *67*, 74–76. (e) Davis, R.; Carroll, A.; Pierens, G.; Quinn, R. *J. Nat. Prod.* **1999**, *62*, 419–424. (f) Marco, E.; Laine, W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. *J. Med. Chem.* **2005**, *48*, 3796–3807.

10.1021/ol3026507
Published on Web 10/22/2012

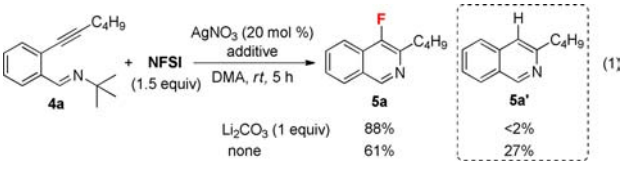
Thus, smuggling fluorine into isoquinoline should be helpful to reduce the metabolism of isoquinolines and adjust its biological activities.[4] Recently, fluorinated isoquinolines have been used as building blocks for the design of pharmaceutical drugs. For instance, 4-fluoroisoquinolines **1**–**3** have been used as antiproliferative drugs, as myosin inhibitors, and for reducing intraocular pressure.[5] However, the synthesis of 4-fluoroisoquinolines is quite rare. These compounds are prepared from electrophilic fluorination by using ^{n}BuLi as a strong base to generate a nucleophilic carbanion to attack the F^+ reagent. Such conditions often result in poor functional group compatibility.[6] For more complex fluorinated heteroarenes, 4-fluoropyrrolo[α]isoquinolines, there is no report for their preparation. As part of our ongoing research program to develop a fluorine-oriented heterocycles synthetic method,[7] we herein report a novel method for the construction of 4-fluoroisoquinolines and 4-fluoropyrrolo-[α]isoquinolines with high efficiency. It is worth noting that all the reactions exhibited excellent regioselectivity favoring fluorine in the 4° carbon position.

Isoquinoline can be efficiently synthesized from transition-metal-catalyzed hydroamination of alkyne, in which an sp^2 C–M bond is involved and prone to protonolysis.[8] In addition, Larock,[9a,b] Li,[9c] and Wu[9d] reported that the related sp^2 C–M bond can be oxidized to form the corresponding halogenated isoquinolines. We envisioned that if the sp^2 C–M bond can be directly fluorinated, a concise pathway should be expected for the synthesis of a fluoroisoquinoline (Scheme 1).

Scheme 1. Proposed Synhesis of Fluoroisoquinoline and Fluoropyrrolo[α]isoquinoline



Recently, transition-metal-catalyzed carbon–fluorine bond formation has emerged as a highly desirable but challenging approach for the synthesis of organofluorines with high efficiency.[10] For instance, Ritter and co-workers have reported a silver-catalyzed oxidative fluorination of arylstannanes using SelectFluor as the fluorinating reagent for arylfluoride synthesis under mild reaction conditions.[11] We have discovered a silver-catalyzed oxidative fluoroamination of allenes to afford a variety of fluorinated dihydropyrroles. Among those transformations, the oxidative fluorination of the sp^2 C–Ag bond by the F^+ reagent have been proposed to address the formation of sp^2 C–F bond.[7d] Inspired by this work, our initial investigation focused on the oxidative fluorination of **4a** by using a silver catalyst. We were delighted that the reaction of **4a** afforded the



desired fluorinated isoquinoline **5a** in the presence of fluorinating reagent NFSI. After screening silver catalysts, solvents, bases, and fluorinating reagents (see the Supporting Information), optimum conditions were obtained for a reaction with 20% $AgNO_3$, 1.5 equiv of NFSI, and 1 equiv of Li_2CO_3 in DMA (*N*,*N*-dimethylacetamide), and the desired product **5a** was produced in 88% ^{19}F NMR yield (eq 1). It is worth noting that the addition of Li_2CO_3 is crucial to inhibit the formation of hydroamination product **5a**′.[12] In addition, the desired product **5a** was not observed in the absence of the silver catalyst.

(4) For the studies on the metabolism of isoquinolines, see: (a) Boyd, D. R.; Sharma, N. D.; Dorrity, M. R. J.; Hand, M. V.; McMordie, R. A. S.; Malone, J. F.; Porter, H. P.; Dalton, H.; Chima, J.; Sheldrake, G. N. *J. Chem. Soc., Perkin. Trans. 1* **1993**, 1065–1071. (b) LaVoie, E. J.; Adams, E. A.; Shigematsu, A.; Hoffmann, D. *Carcinogenesis* **1983**, *4*, 1169–1173.

(5) For some recent patents involving fluorinated isoquinolines, see: (a) Yamada, R.; Seto, M. U.S. Patent 201093789, 2010. (b) Zeng, Q.; Yuan, C. C.; Yao, G.; Wang, X.; Tadesse, S.; Jean JR, D. J. S.; Reichelt, A.; Liu, Q.; Hong, F.-T.; Han, N.; Fotsch, C.; Davis, C.; Bourbeau, M. P.; Ashton, K. S.; Allen, J. G. WO 201083246, 2010. (c) Matsubara, K.; Iesato, A.; Oomura, A.; Kawasaki, K.; Yamada, R.; Seto, M. U.S. Patent 200948223 A1, 2009.

(6) Only two examples of 4-fluoroisoquinolines were reported from 2-methylaniline by using BuLi; see: Si, C.; Myers, A. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 10409–10413.

(7) (a) Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354–16355. (b) Peng, H.; Liu, G. *Org. Lett.* **2011**, *13*, 772–775. (c) Xu, T.; Qiu, S.; Liu, G. *Chin. J. Chem.* **2011**, *29*, 2785–2790. (d) Xu, T.; Mu, X.; Peng, H.; Liu, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 8176–8179. (e) Mu, X.; Liu, G. *Chem.—Eur. J.* **2011**, *17*, 6039–6042. (f) Mu, X.; Wu, T.; Wang, H.-Y.; Guo, Y.-L.; Liu, G. *J. Am. Chem. Soc.* **2012**, *134*, 878–881.

(8) For some reviews, see: (a) Majumdar, K. C.; Debnath, P.; De, N.; Roy, B. *Curr. Org. Chem.* **2011**, *15*, 1760–1801. (b) Montalban, A. G. *Heterocycl. Nat. Prod. Synth.* **2011**, 299–339. (c) Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Commun.* **2009**, 5075–5087. (d) Fulop, F.; Bernath, G. *Curr. Org. Chem.* **1999**, *3*, 1–24. For selected examples, see: (e) Zheng, D.; Chen, Z.; Wu, J.; Liu, J. *Org. Biomol. Chem.* **2011**, *9*, 4763–4765. (f) Gao, H.; Zhang, J. *Adv. Synth. Catal.* **2009**, *351*, 85–88. (g) Asao, N.; Salprima, Y. S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526–5528. (h) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 980–988.

(9) (a) Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920–928. (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437–3444. (c) Zhang, H.-P.; Yu, S.-C.; Liang, Y.; Peng, P.; Tang, B.-X.; Li, J.-H. *Synlett* **2011**, *2011*, 982–988. (d) Yu, X.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 895–899.

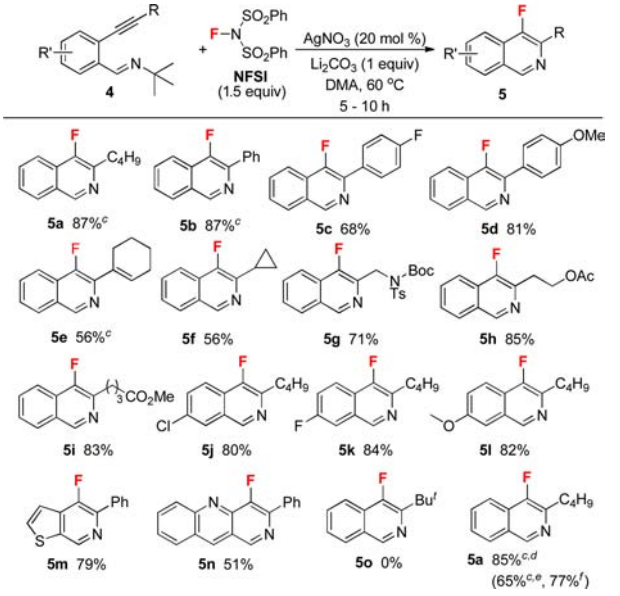
(10) For some recent reviews on the transition-metal-catalyzed fluoriantion, see: (a) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160–171. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470–477. (c) Vigalok, A. *Organometallics* **2011**, *30*, 4802–4810. (d) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, *48*, 2929–2942. (e) Liu, G. *Org. Biomol. Chem.* **2012**, *10*, 6243–6248.

(11) For silver-catalyzed fluorination involving oxidative fluorination of an aryl C–Ag bond, see: Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150–12152 and references therein.

(12) The hydroamination product **5a**′ is resulted from the protonolysis Aryl-Ag intermediate by the proton generated from the elimination of the isobutyl group. The role of Li_2CO_3 is to neutralize the proton.

Under our standard conditions, the substrate scope of the amino-fluorination reaction was then examined (Table 1). A variety of functional groups on the alkyne were compatible with the reaction conditions. For instance, substrates possessing alkyl, aryl, vinyl, and cyclopropyl groups exhibited good reactivity to afford the corresponding fluorinated isoquinolines **5a**–**5f** in good yields. Note that both imide (**4g**) and ester (**4h**–**4i**) groups, which are sensitive to BuLi, were tolerated in the reaction. Substrates with different functional groups in aryl ring were also tested. A series of substituted groups, such as a halogen (**4j**–**4k**) or ether (**4l**), were productive in this transformation and gave desired products in good yields. To our delight, the heterocycle substrates **4m**–**4n** were also successfully processed to generate fluorinated heterocycles. But substrate **4o** bearing a *tert*-butyl group is unable to afford the cyclization product. Furthermore, reaction of **4a** still afforded the product **5a** in excellent yield (85%) when the reaction was enlarged to 1 mmol scale. Finally, the reaction was examined in a short time, and a satisfactory yield (65% or 77%) was obtained in the high catalyst loading (1.5 equiv of $AgNO_3$ for 30 min at rt) or high temperature (0.2 equiv of $AgNO_3$ for 10 min at 70 °C). This fast reaction provides the possibility to synthesize F^{18} labeled fluoroisoquinolines for application of PET imaging.[13]

Table 1. Silver-Catalyzed Aminofluorination of Alkyne[a,b]



[a] Reaction conditions: substrate **4** (0.2 mmol), $AgNO_3$ (20 mol %), NFSI (1.5 equiv), Li_2CO_3 (1 equiv), DMA (3 mL), rt. [b] Isolated yield. [c] NFSI (1.5 equiv) at 30 °C. [d] 1 mmol scale. [e] $AgNO_3$ (1.5 equiv), 30 min. [f] $AgNO_3$ (20 mol %), NFSI (1.5 equiv), 10 min, 70 °C.

Scheme 2. Silver-Catalyzed Tandem Fluorination and [3 + 2] Dipolar Cycloaddition

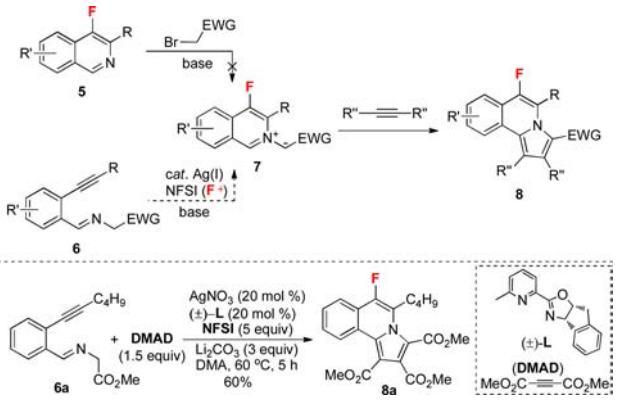
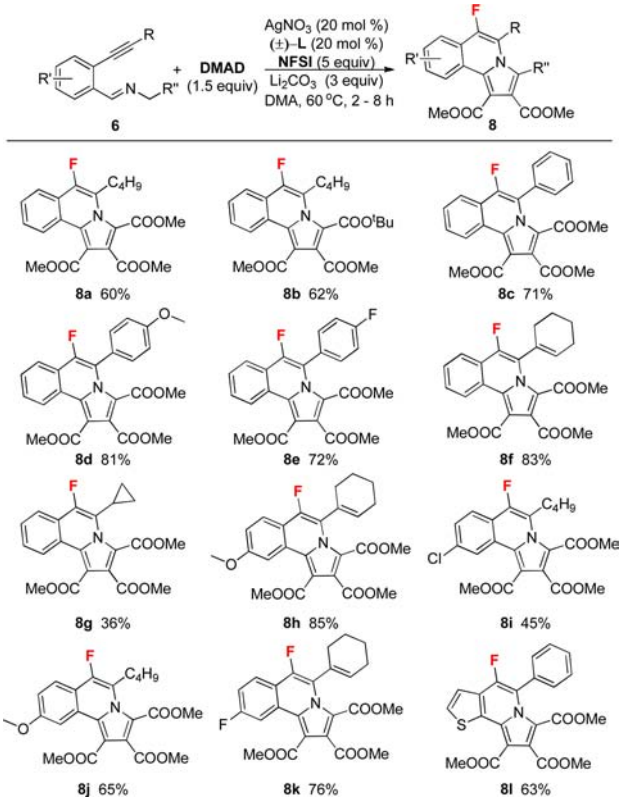


Table 2. Silver-Catalyzed Tandem Aminofluorination of Alkynes and [3 + 2] Dipolar Cycloaddition[a]



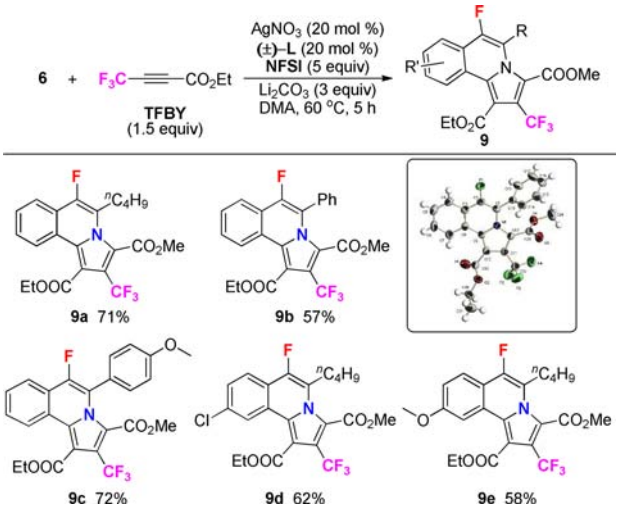
[a] All reactions were conducted on 0.2 mmol scale, and isolated yields were given.

Isoquinonlines have been extensively used to conduct [2 + 3] dipolar cycloadditions for the synthesis of

(13) (a) Littich, R.; Scott, P. J. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1106–1109. (b) Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. *Science* **2011**, *334*, 639–642. (c) Teare, H.; Robins, E. G.; Kirjavainen, A.; Forsback, S.; Sandford, G.; Solin, O.; Luthra, S. K.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 6821–6824.

(14) For reviews on the silver-catalyzed dipolar cycloaddition, see: (a) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132–3148. (b) Alvarez-Corral, M.; Munoz-Dorado, M.; Rodirguez-Garcia, I. *Chem. Rev.* **2008**, *108*, 3174–3198.

Table 3. Silver-Catalyzed Tandem Reaction **6** with Trifluoromethyl Butyroate[a]



[a] All reactions were conductd on 0.2 mmol scale, and isolated yields were given.

pyrrolo-[α]isoquinolines.[14] Following this principle, we wondered if the fluorinated pyrrolo[α]isoquinolines **8** could be generated from fluorinated isoquinolines **5**. Unfortunately, the [2 + 3] dipolar cycloaddition of 4-fluoroisoquinolines **5a** does not proceed to afford **8** because the intermediate **7** could not be generated from **5** due to the weak nucleophilic ability.[15] We hypothesized that the intermediate **7** might be generated *in situ* from alkynylenamine **6**, followed by dipolar cycloaddition to achieve a fluorinated pyrrolo[α]isoquinoline synthesis (Scheme 2, top). We were delighted that the tandem reaction of **6a** with dimethyl acetylene dicarboxylate (DMAD) could be catalyzed by $AgNO_3$ with a bidental nitrogen ligand to afford the desired product **8a** in 60% isolated yield (Scheme 2, bottom).[16]

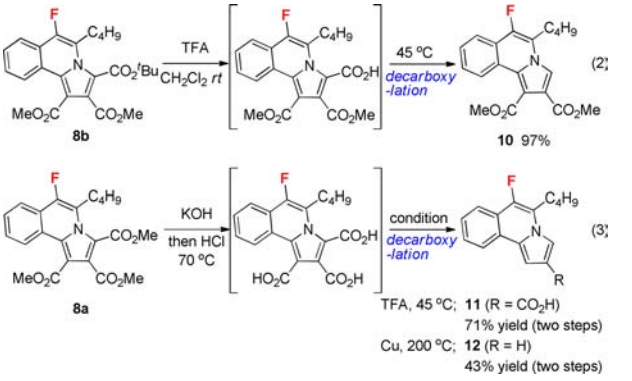
As shown in Table 2, the reaction has a broad substrate scope. It was the same with substrate **6a**, the reaction of *tert*-butyl ester **6b** provided the desired product in good yield (62%). The substrates bearing alkyl, aryl, and vinyl groups on the alkyne afforded the corresponding cycloaddition products **8a**–**8f** in moderate to good yields. Among them, substrate **6f** bearing a cyclohexene group gave the best yield. In contrast, a substrate with a cyclopropyl group delivered a slightly lower yield (**8g**). Furthermore, several functional groups in the aromatic ring, such as a halide and methoxy, were compatible with the catalytic system to generate desired products **8h**–**8k** in good yields. It is worth noting that the bisheteroatom-containing fluorocycle **8l** can be efficiently synthesized.

(15) The weak nucleophilic ability of the nitrogen atom is the result of the strong electronegativity of fluorine.

(16) For the screening results, see the Supporting Information.

In addition, we were delighted to learn that the electron-deficient ethyl 4,4,4-trifluorobutynate (**TFBY**) exhibited good reactivity to afford single product **9** with excellent regioselectivity (Table 3). The structure of **9b** was characterized by X-ray. This methodology presents one of most efficient ways to introduce both a fluorine and CF_3 group simultaneously to heterocycle compounds.

Finally, further transformation of compound **8** was explored via a decarboxylation process. The fluorinated pyrrolo[α]isoquinolines lacking carboxylates can be prepared. For example, compound **8b** was treated by trifluoroacetic acid (TFA) to remove the *tert*-butyl group and then underwent decarboxylation to give diester **10** in quantitative yield (eq 2). Meanwhile, **8a** was hydrolyzed in aqueous KOH to give a triacid intermediate, which participated in sequential decarboxylation with TFA to afford **11** in 71% yield. Alternatively, the decarboxylation could be accomplished with copper at high temperature to generate **12** in 43% yield (eq 3).



In conclusion, we have developed a novel silver-catalyzed intramolecular oxidative aminofluorination of alkynes. This methodology efficiently provides 4-fluoroisoquinolines and 4-fluoropyrrolo[α]isoquinolines. It enriches the methods available for the synthesis of these fluoroheterocycles and potentially promotes their application in drug discovery. 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. 20972175, 20923005, and 21121062), the Science and Technology Commission of the Shanghai Municipality (11JC1415000), and the Chinese Academy of Sciences.

Supporting Information Available. Detail experimental procedures and analytical 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.