ChemInform Abstract: Facile Assembly of 1-[(Trifluoromethyl)thio]isoquinolines Through Reaction of 2-Alkynylbenzaldoxime with Silver (Trifluoromethyl)thiolate.

ARTICLE *in* EUROPEAN JOURNAL OF ORGANIC CHEMISTRY · JUNE 2014

Impact Factor: 3.07 · DOI: 10.1002/ejoc.201301401

4 AUTHORS, INCLUDING:

Qiuping Ding
Jiangxi Normal University
100 PUBLICATIONS **1,638** CITATIONS

SEE PROFILE

EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201301401

Facile Assembly of 1-[(Trifluoromethyl)thio]isoquinolines through Reaction of 2-Alkynylbenzaldoxime with Silver (Trifluoromethyl)thiolate

Qing Xiao,[a] Jie Sheng,[b] Qiuping Ding,*[a] and Jie Wu*[b,c]

Keywords: Synthetic methods / Nitrogen heterocycles / Alkynes / Silver / Fluorine / Sulfur

1-[(Trifluoromethyl)thio]isoquinolines can be assembled through silver(I)-catalyzed reaction of 2-alkynylbenzaldoxime with silver (trifluoromethyl)thiolate in the presence of *p*-methoxybenzenesulfonyl chloride. The (trifluoromethyl)thio moiety (SCF_3) could be easily introduced into the scaffold of isoquinoline under mild conditions.

Introduction

The importance of isoquinolines in synthetic organic chemistry and pharmaceuticals is well-recognized,[1,2] and this privileged scaffold is present in a broad range of natural products and drug molecules. Compounds with the core of isoquinoline often show remarkable biological activities. In the meantime, due to the increasing interest in fluorine chemistry,[3] the construction of fluorinated heterocycles has attracted growing attention recently.[4] Among the N-heterocycles, fluorinated isoquinolines have served as building blocks for the design and synthesis of biologically active compounds, including antiproliferative drugs, myosin inhibitors, and agents for reducing intraocular pressure.[5] Therefore, continuous efforts have focused on the synthesis of fluorinated isoquinolines.[6] For example, Liu and coworkers reported the generation of 4-fluoroisoquinolines through a silver-catalyzed intramolecular oxidative aminofluorination of alkynes by using *N*-fluorobenzenesulfonimide (NSFI) as the fluorine source (Figure 1).[6a] From the viewpoint of studies of chemical genetics using natural product-like compounds, a biological evaluation of the use of diverse fluorinated isoquinolines would be beneficial.

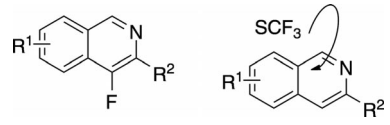


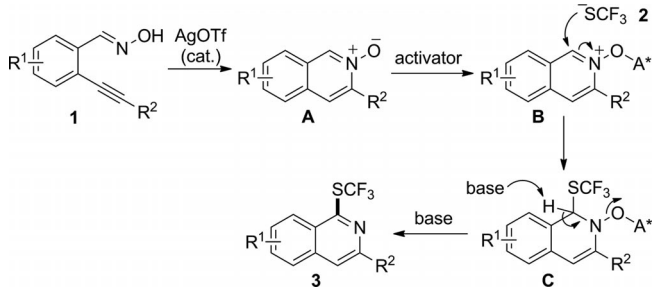
Figure 1. Fluorinated isoquinolines.

In the past few years, the introduction of a (trifluoromethyl)thio moiety (SCF_3) into small molecules has been a hot field in fluorine chemistry.[7,8] The attractive intrinsic properties of this group (such as its high lipophilicity) has prompted its rapid development. For instance, Billard reported the electrophilic trifluoromethanesulfanylation of organometallic species with trifluoromethanesulfanamides for C–SCF_3 bond formation.[7b] Aryl trifluoromethyl thioethers could be synthesized through trifluoromethylthiolation of aryl boronic acids with $TMSCF_3$ and elemental sulfur or by using $AgSCF_3$ in coupling reactions.[7c,7f] Because (trifluoromethyl)thio-substituted compounds are usually used as candidates in pharmaceutical and agrochemical applications, we became interested in the introduction of the (trifluoromethyl)thio moiety into the scaffold of isoquinoline (Figure 1).

Recently, the reactivity of 2-alkynylbenzaldoxime has been extensively explored, and these studies have provided a facile route to isoquinoline derivatives.[9] For example, 1-aryloxyisoquinolines could be generated through silver-catalyzed reaction of 2-alkynylbenzaldoxime with phenols.[9d] During the transformation, a phosphonium salt or sulfonyl chloride was essential for the activation of the *N*-oxide formed in situ. In light of these results, we hypothesized that a silver-catalyzed reaction of 2-alkynylbenzaldoxime with $AgSCF_3$[10] might allow the formation of (trifluoromethyl)thio-substituted isoquinolines under suitable conditions. The proposed synthetic route is presented in Scheme 1.

[a] Key Laboratory of Functional Small Organic Molecules, Ministry of Education and College of Chemistry & Chemical Engineering, Jiangxi Normal University, Nanchang, Jiangxi 330022, China
E-mail: dqpjxnu@gmail.com
[b] Department of Chemistry, Fudan University, 220 Handane Road, Shanghai 200433, China
E-mail: jie_wu@fudan.edu.cn
http://www.chemistry.fudan.edu.cn/teacher.asp?tno=wujie
[c] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301401.

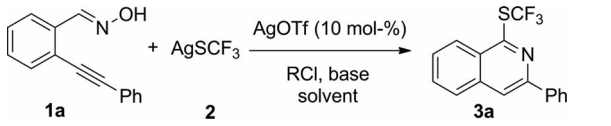


Scheme 1. The proposed route to (trifluoromethyl)thio-substituted isoquinolines.

Results and Discussion

The initial studies were carried out for the reaction of 2-alkynylbenzaldoxime **1a** with $AgSCF_3$ (**2**) catalyzed by 10 mol-% silver triflate in the presence of iPr_2NEt (DIPEA) in 1,4-dioxane (Table 1). Initially, a range of activators including acid chloride, sulfonyl chloride, and phosphonyl chloride were evaluated. However, no reaction took place when acetic acid chloride was used (Table 1, entry 1). The result was not improved when PhCOCl, *t*BuCOCl, or Ph_2POCl were employed (Table 1, entries 2–4). To our delight, the desired 1-[(trifluoromethyl)thio]isoquinoline **3a** was obtained in 16% yield when benzenesulfonyl chloride was added in the reaction (Table 1, entry 5). Other sulfonyl chlorides were then screened (Table 1, entries 6–9), and it was found that the addition of *p*-$MeOC_6H_4SO_2Cl$ gave the best result (27% yield; Table 1, entry 7). Further screening of solvents revealed that the reaction proceeded efficiently in *N*,*N*-dimethylacetamide (DMA), leading to the expected product **3a** in 55% yield (Table 1, entry 17). The reaction was subsequently examined in the presence of various bases (Table 1, entries 18–26). Gratifyingly, the desired product **3a** was generated in 87% yield when the reaction was performed in the presence of K_3PO_4 (Table 1, entry 21).

Table 1. Initial optimization of the reaction of 2-alkynylbenzaldoxime **1a** with $AgSCF_3$ (**2**).[a]

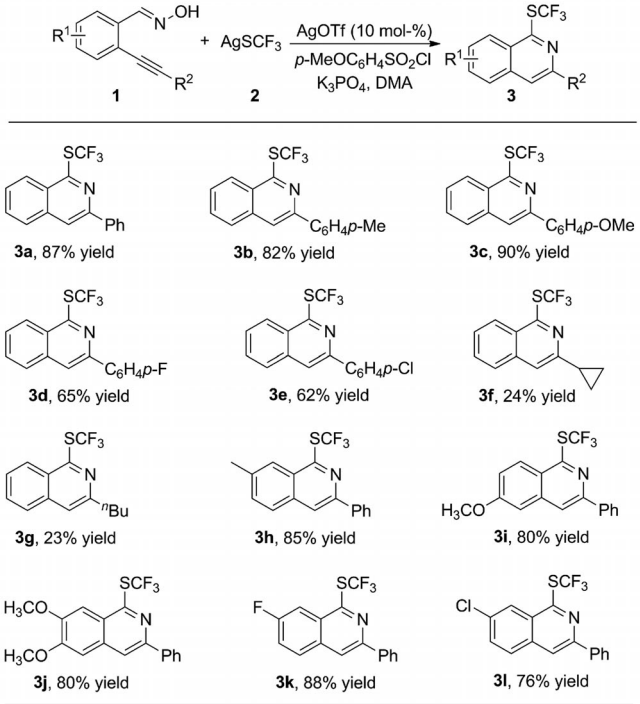


Entry	RCl	Base	Solvent	Yield [%][b]
1	CH_3COCl	DIPEA	1,4-dioxane	n.r.
2	PhCOCl	DIPEA	1,4-dioxane	5
3	*t*BuCOCl	DIPEA	1,4-dioxane	n.r.
4	Ph_2POCl	DIPEA	1,4-dioxane	n.r.
5	$PhSO_2Cl$	DIPEA	1,4-dioxane	16
6	TsCl	DIPEA	1,4-dioxane	20
7	*p*-$MeOC_6H_4SO_2Cl$	DIPEA	1,4-dioxane	27
8	*p*-$NO_2C_6H_4SO_2Cl$	DIPEA	1,4-dioxane	5
9	MsCl	DIPEA	1,4-dioxane	10
10	*p*-$MeOC_6H_4SO_2Cl$	DIPEA	CH_2Cl_2	45
11	*p*-$MeOC_6H_4SO_2Cl$	DIPEA	DCE	44
12	*p*-$MeOC_6H_4SO_2Cl$	DIPEA	THF	38
13	*p*-$MeOC_6H_4SO_2Cl$	DIPEA	toluene	35
14	*p*-$MeOC_6H_4SO_2Cl$	DIPEA	MeCN	44
15	*p*-$MeOC_6H_4SO_2Cl$	DIPEA	DMSO	26
16	*p*-$MeOC_6H_4SO_2Cl$	DIPEA	DMF	50
17	*p*-$MeOC_6H_4SO_2Cl$	DIPEA	DMA	55
18	*p*-$MeOC_6H_4SO_2Cl$	Et_3N	DMA	56
19	*p*-$MeOC_6H_4SO_2Cl$	Cs_2CO_3	DMA	44
20	*p*-$MeOC_6H_4SO_2Cl$	DBU	DMA	44
21	*p*-$MeOC_6H_4SO_2Cl$	K_3PO_4	DMA	87
22	*p*-$MeOC_6H_4SO_2Cl$	NaOAc	DMA	46
23	*p*-$MeOC_6H_4SO_2Cl$	Na_2CO_3	DMA	50
24	*p*-$MeOC_6H_4SO_2Cl$	$NaHCO_3$	DMA	42
25	*p*-$MeOC_6H_4SO_2Cl$	pyridine	DMA	39
26	*p*-$MeOC_6H_4SO_2Cl$	*t*BuOK	DMA	n.r.

[a] Reaction conditions: **1a** (0.2 mmol), AgOTf (10 mol-%), $AgSCF_3$ **2** (0.3 mmol), base (0.9 mmol), RCl (0.3 mmol), solvent (2.0 mL), 25 °C. [b] Isolated yield based on **1a**; n.r.: no reaction.

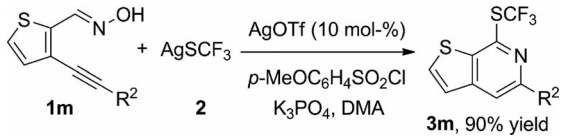
The generality of this silver(I)-catalyzed reaction of 2-alkynylbenzaldoxime with silver (trifluoromethyl)thiolate in the presence of *p*-methoxybenzenesulfonyl chloride was then examined under the optimized conditions. The results are shown in Table 2. A range of 1-[(trifluoromethyl)thio]-isoquinolines could be produced as expected. The nature of the substituents on the triple bond of the 2-alkynylbenzaldoximes affected the final outcome. 2-Alkynylbenzaldoximes with a range of aryl groups attached on the triple bond reacted with silver (trifluoromethyl)thiolate smoothly, giving the corresponding products in good yields. However, the yields were low when the aryl group attached on the triple bond was replaced by an alkyl group. For instance, cyclopropyl-substituted 1-[(trifluoromethyl)thio]isoquin-

Table 2. Synthesis of 1-[(trifluoromethyl)thio]isoquinolines through silver-catalyzed reaction of 2-alkynylbenzaldoxime **1** with $AgSCF_3$ (**2**).[a,b]



[a] Reaction conditions: 2-alkynylbenzaldoxime **1** (0.2 mmol), AgOTf (10 mol-%), $AgSCF_3$ **2** (0.3 mmol), K_3PO_4 (0.9 mmol), *p*-$MeOC_6H_4SO_2Cl$ (0.3 mmol), DMA (2.0 mL), 25 °C. [b] Isolated yield based on **1**.

oline **3f** was formed in 24% yield, and compound **3g**, with an *n*-butyl group, was obtained in 23% yield. This might be due to the reactivity of the alkyl-substituted substrates, since the reaction did not go to completion and was stopped at the isoquinoline *N*-oxide stage. With respect to substrates with substituents on the aromatic ring of 2-alkynylbenzaldoximes, all reactions worked well under the standard conditions, leading to the desired products in good yields. Interestingly, thiophenyl-incorporated substrate **1m** was also found to be a good reactant, affording the corresponding product **3m** in 90% yield (Scheme 2).



Scheme 2. Reaction of compound **1m** with $AgSCF_3$. Reaction conditions: 3-(phenylethynyl)thiophene-2-carbaldehyde oxime (**1m**; 0.2 mmol), AgOTf (10 mol-%), $AgSCF_3$ **2** (0.3 mmol), K_3PO_4 (0.9 mmol), *p*-$MeOC_6H_4SO_2Cl$ (0.3 mmol), DMA (2.0 mL), 25 °C.

Conclusions

We have reported a facile assembly of 1-[(trifluoromethyl)thio]isoquinolines through silver(I)-catalyzed reaction of 2-alkynylbenzaldoxime with silver (trifluoromethyl)thiolate in the presence of *p*-methoxybenzenesulfonyl chloride. The (trifluoromethyl)thio moiety (SCF_3) could be easily introduced into the scaffold of isoquinoline under mild conditions. Further exploration of the utility of $AgSCF_3$ for the generation of other fluorinated N-heterocycles is ongoing in our laboratory.

Experimental Section

General Procedure for the synthesis of 1-[(trifluoromethyl)thio]isoquinolines: 2-Alkynylbenzaldoxime **1** (0.2 mmol) was added to a solution of AgOTf (10 mol-%) in DMA (1.0 mL) under N_2. After stirring at 70 °C for 1 h, $AgSCF_3$ **2** (0.3 mmol), K_3PO_4 (0.9 mmol), and *p*-$MeOC_6H_4SO_2Cl$ (0.3 mmol) were added followed by DMA (1.0 mL). The mixture was stirred at 25 °C until completion of reaction (indicated by TLC analysis; typically overnight), then the mixture was purified by flash column chromatograph (EtOAc/*n*-hexane, 1:100) to give the desired product **3**.

3-Phenyl-1-[(trifluoromethyl)thio]isoquinoline (3a): Yield 53.0 mg (87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20–8.15 (m, 3 H), 8.06 (s, 1 H), 7.90 (d, J = 8.0 Hz, 1 H), 7.75–7.71 (m, 1 H), 7.64–7.60 (m, 1 H), 7.53–7.50 (m, 2 H), 7.45–7.41 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 138.0, 137.4, 131.1, 129.3 (q, J = 301.6 Hz), 129.1, 128.9, 127.9, 127.8, 126.8, 124.9, 121.6, 116.2 ppm. ^{19}F NMR (378 MHz, $CDCl_3$): δ = –39.13 ppm. HRMS (ESI): calcd. for $C_{16}H_{10}F_3NS^+$ [M + H$^+$] 306.0559; found 306.0586.

3-(*p*-Tolyl)-1-[(trifluoromethyl)thio]isoquinoline (3b): Yield 53.5 mg (82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.03 (m, 3 H), 7.92 (m, 1 H), 7.77 (d, J = 8.0 Hz, 1 H), 7.63 (t, J = 7.6 Hz, 1 H), 7.52 (t, J = 7.6 Hz, 1 H), 7.26 (d, J = 7.6 Hz, 2 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7, 150.3, 139.1, 137.5, 135.3, 129.6, 129.3 (q, J = 307.2 Hz), 127.8, 127.7, 127.4, 126.7, 124.9, 124.7, 115.7, 21.9 ppm. ^{19}F NMR (378 MHz, $CDCl_3$): δ = –39.07 ppm. HRMS (ESI): calcd. for $C_{17}H_{13}F_3NS^+$ [M + H$^+$] 320.0715; found 320.0715.

3-(4-Methoxyphenyl)-1-[(trifluoromethyl)thio]isoquinoline (3c): Yield 60.4 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (m, 3 H), 7.91 (s, 1 H), 7.81 (d, J = 8.0 Hz, 1 H), 7.66 (t, J = 7.2 Hz, 1 H), 7.54 (t, J = 7.6 Hz, 1 H), 6.00 (d, J = 8.8 Hz, 2 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 150.5, 150.3, 137.6, 131.0, 130.7, 129.3 (q, J = 307.2 Hz), 128.1, 127.7, 127.5, 127.1, 124.9, 115.0, 114.2, 55.4 ppm. ^{19}F NMR (378 MHz, $CDCl_3$): δ = –39.12 ppm. HRMS (ESI): calcd. for $C_{17}H_{13}F_3NOS^+$ [M + H$^+$] 336.0664; found 336.0662.

3-(4-Fluorophenyl)-1-[(trifluoromethyl)thio]isoquinoline (3d): Yield 42.0 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14–8.07 (m, 3 H), 7.91 (s, 1 H), 7.82 (d, J = 8.0 Hz, 1 H), 7.68 (t, J = 7.2 Hz, 1 H), 7.59–7.55 (m, 1 H), 7.15 (t, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5 (d, J = 247.3 Hz), 150.6, 149.6, 134.2, 131.1, 129.2 (q, J = 310.9 Hz), 128.5 (q, J = 6.2 Hz), 127.9 (d, J = 18.5 Hz), 127.2, 124.7 (d, J = 20.7 Hz), 115.7 (d, J = 11.0 Hz), 115.6 (d, J = 11.5 Hz) ppm. ^{19}F NMR (378 MHz, $CDCl_3$): δ = –39.13, –133.25 (Ar-F) ppm. HRMS (ESI): calcd. for $C_{16}H_{10}F_4NS^+$ [M + H$^+$] 324.0465; found 324.0458.

3-(4-Chlorophenyl)-1-[(trifluoromethyl)thio]isoquinoline (3e): Yield 42.0 mg (62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13–8.09 (m, 3 H), 7.98 (s, 1 H), 7.87 (d, J = 8.0 Hz, 1 H), 7.74–7.71 (m, 1 H), 7.64–7.60 (m, 1 H), 7.46–7.44 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.8, 149.4, 137.3, 136.5, 135.1, 131.2, 129.2 (q, J = 300.7 Hz), 129.0, 128.2, 128.0, 127.9, 124.9, 116.1 ppm. ^{19}F NMR (378 MHz, $CDCl_3$): δ = –39.13 ppm. HRMS (ESI): calcd. for $C_{16}H_{10}ClF_3NS^+$ [M + H$^+$] 340.0169; found 340.0165.

3-Cyclopropyl-1-[(trifluoromethyl)thio]isoquinoline (3f): Yield 13.0 mg (24%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.4 Hz, 1 H), 7.72 (d, J = 8.4 Hz, 1 H), 7.66–7.63 (m, 1 H), 7.52–7.48 (m, 1 H), 7.46 (s, 1 H), 2.15–2.08 (m, 1 H), 1.17–1.14 (m, 2 H), 1.03–0.99 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 137.1, 130.7, 129.6 (q, J = 300.7 Hz), 126.7, 126.6, 124.8, 117.1, 16.6, 9.7 ppm. ^{19}F NMR (378 MHz, $CDCl_3$): δ = –39.22 ppm. HRMS (ESI): calcd. for $C_{13}H_{11}F_3NS^+$ [M + H$^+$] 270.0559; found 270.0552.

3-*n*-Butyl-1-[(trifluoromethyl)thio]isoquinoline (3g): Yield 12.5 mg (23%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J = 8.4 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.72–7.68 (m, 1 H), 7.62–7.58 (m, 1 H), 7.50 (s, 1 H), 2.96 (t, J = 7.6 Hz, 2 H), 1.85–1.77 (m, 2 H), 1.45–1.36 (m, 2 H), 0.95 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 137.5, 130.7, 129.3 (q, J = 300.7 Hz), 127.4, 126.9, 125.8, 119.5, 37.4, 31.7, 22.3, 13.9 ppm. ^{19}F NMR (378 MHz, $CDCl_3$): δ = –39.45 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}F_3NS^+$ [M + H$^+$] 286.0872; found 286.0854.

7-Methyl-3-phenyl-1-[(trifluoromethyl)thio]isoquinoline (3h): Yield 54.4 mg (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16–8.14 (m, 2 H), 7.95 (s, 1 H), 7.86 (s, 1 H), 7.73 (d, J = 8.4 Hz, 1 H), 7.51–7.46 (m, 3 H), 7.40 (t, J = 7.2 Hz, 1 H), 2.53 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 149.5, 138.3, 138.2, 135.7, 133.3, 129.4 (q, J = 300.7 Hz), 128.8, 127.6, 126.6, 123.7, 116.1, 22.0 ppm. ^{19}F NMR (378 MHz, $CDCl_3$): δ = –39.09 ppm. HRMS (ESI): calcd. for $C_{17}H_{13}F_3NS^+$ [M + H$^+$] 320.0715; found 320.0707.

6-Methoxy-3-phenyl-1-[(trifluoromethyl)thio]isoquinoline (3i): Yield 53.7 mg (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16–8.14 (m, 2 H), 8.04 (d, J = 9.2 Hz, 1 H), 7.92 (s, 1 H), 7.50–7.47 (m, 2 H),

7.43–7.39 (m, 1 H), 7.21–7.19 (m, 1 H), 7.08 (d, J = 2.4 Hz, 1 H), 3.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 151.2, 149.6, 139.7, 138.2, 129.4 (q, J = 306.9 Hz), 129.0, 128.8, 127.0, 126.8, 123.6, 120.9, 115.9, 105.3, 55.6 ppm. ^{19}F NMR (378 MHz, $CDCl_3$): δ = –39.10 ppm. HRMS (ESI): calcd. for $C_{17}H_{13}F_3NOS^+$ [M + H$^+$] 336.0664; found 336.0658.

6,7-Dimethoxy-3-phenyl-1-[(trifluoromethyl)thio]isoquinoline (3j): Yield 58.6 mg (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, J = 7.6 Hz, 2 H), 7.86 (s, 1 H), 7.46 (t, J = 7.2 Hz, 2 H), 7.40–7.37 (m, 2 H), 7.05 (s, 1 H), 4.02 (s, 3 H), 4.00 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5, 150.9, 149.8, 146.7, 138.3, 134.4, 129.5 (q, J = 307.2 Hz), 128.8, 128.7, 126.5, 124.6, 115.9, 105.5, 103.6, 56.2 ppm. ^{19}F NMR (378 MHz, $CDCl_3$): δ = –39.11 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}F_3NO_2S^+$ [M + H$^+$] 366.0770; found 366.0774.

7-Fluoro-3-phenyl-1-[(trifluoromethyl)thio]isoquinoline (3k): Yield 57.0 mg (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14–8.12 (m, 2 H), 8.00 (s, 1 H), 7.88–7.85 (m, 1 H), 7.79–7.76 (m, 1 H), 7.51–7.45 (m, 3 H), 7.43–7.39 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1 (d, J = 250.1 Hz), 150.5, 149.5, 137.7, 134.6, 130.5 (d, J = 8.6 Hz), 129.2, 129.1 (q, J = 307.8 Hz), 128.9, 128.5 (d, J = 8.5 Hz), 126.7, 116.2, 109.1 (d, J = 22.8 Hz) ppm. ^{19}F NMR (378 MHz, $CDCl_3$): δ = –39.16, –108.8 (Ar-F) ppm. HRMS (ESI): calcd. for $C_{16}H_{10}F_4NS^+$ [M + H$^+$] 324.0465; found 324.0458.

7-Chloro-3-phenyl-1-[(trifluoromethyl)thio]isoquinoline (3l): Yield 51.7 mg (76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16–8.15 (m, 3 H), 78.03 (s, 1 H), 7.84 (d, J = 8.8 Hz, 1 H), 7.68–7.65 (m, 1 H), 7.53–7.49 (m, 2 H), 7.46–7.42 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 149.5, 137.6, 135.8, 132.7, 132.2, 129.4, 129.3, 129.0 (q, J = 300.7 Hz), 128.9, 128.6, 126.8, 124.2, 115.9 ppm. ^{19}F NMR (378 MHz, $CDCl_3$): δ = –39.10 ppm. HRMS (ESI): calcd. for $C_{16}H_{10}ClF_3NS^+$ [M + H$^+$] 340.0169; found 340.0155.

5-Phenyl-7-[(trifluoromethyl)thio]thieno[2,3-*c*]pyridine (3m): Yield 56.0 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.07 (m, 3 H), 7.71 (d, J = 5.6 Hz, 1 H), 7.50–7.46 (m, 2 H), 7.43–7.40 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 147.3, 141.8, 139.3, 138.3, 131.2, 129.3 (q, J = 308.2 Hz), 129.1, 128.9, 126.9, 124.1, 114.7 ppm. ^{19}F NMR (378 MHz, $CDCl_3$): δ = –38.89 ppm. HRMS (ESI): calcd. for $C_{14}H_9F_3NS_2^+$ [M + H$^+$] 312.0123; found 312.0114.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of **3**.

Acknowledgments

Financial support from the National Natural Science Foundation of China (NSFC) (grant numbers 21032007, 21172038) is gratefully acknowledged.

[1] a) K. W. Bentley, in: *The Isoquinoline Alkaloids*, Hardwood Academic, Amsterdam, **1998**; b) F. Dzierszinski, A. Coppin, M. Mortuaire, E. Dewally, C. Slomianny, J.-C. Ameisen, F. DeBels, S. Tomavo, *Antimicrob. Agents Chemother.* **2002**, *46*, 3197; c) L. Kong, C. Cheng, R. Tan, *Planta Med.* **2001**, *67*, 74; d) R. Davis, A. Carroll, G. Pierens, R. Quinn, *J. Nat. Prod.* **1999**, *62*, 419; e) E. Marco, W. Laine, C. Tardy, A. Lansiaux, M. Iwao, F. Ishibashi, C. Bailly, F. Gago, *J. Med. Chem.* **2005**, *48*, 3796.

[2] For reviews, see: a) J. Montgomery, *Angew. Chem.* **2004**, *116*, 3980; *Angew. Chem. Int. Ed.* **2004**, *43*, 3890; b) J. Panteleev, L. Zhang, M. Lautens, *Angew. Chem.* **2011**, *123*, 9255; *Angew. Chem. Int. Ed.* **2011**, *50*, 9089; c) S. H. Kim, S. H. Park, J. H. Choi, S. Chang, *Chem. Asian J.* **2011**, *6*, 2618; d) P. Lu, Y. Wang, *Chem. Soc. Rev.* **2012**, *41*, 5687; e) T. Miura, M. Murakami, *Chem. Commun.* **2007**, 217; f) M. Malacria, *Chem. Rev.* **1996**, *96*, 289; g) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551; h) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; i) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; j) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis* Wiley-VCH, Weinheim, Germany, **2006**; k) L. F. Tietze, M. A. Düfert, T. Hungerland, K. Oum, T. Lenzer, *Chem. Eur. J.* **2011**, *17*, 8452.

[3] a) R. Filler, Y. Kobayashi, in: *Biomedicinal Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, **1982**; b) In *Fluorine, in: Bioorganic Chemistry* (Eds.: J. T. Welch, S. Eswarakrishman), Wiley: New York, **1991**; c) *Bioorganic and Medicinal Chemistry of Fluorine* (Eds.: J.-P. Begue, D. Bonnet-Delpon), Wiley, Hoboken, **2008**.

[4] For some reviews on the synthesis of fluorinated heterocycles, see: a) V. A. Petrov, in: *Fluorinated Heterocyclic Compounds: Synthesis Chemistry, and Applications*, John Wiley & Sons, Inc., Hoboken, NJ, **2009**; b) E. V. Nosova, G. N. Lipunova, V. N. Charushin, Q. N. Chupakhin, *J. Fluorine Chem.* **2010**, *131*, 1267; c) S. Zhu, Y. Wang, W. Peng, L. Song, G. Jin, *Curr. Org. Chem.* **2002**, *6*, 1057; d) M. J. Silvester, *Aldrichim. Acta* **1991**, *24*, 31. For some selective examples, see: e) P. Kwiatkowski, T. D. Beeson, J. C. Conrad, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 1738; f) Y. Kishi, H. Nagura, S. Inagi, T. Fuchigami, *Chem. Commun.* **2008**, 3876; g) S. Fustero, S. Catalan, M. Sanchez-Rosello, A. Simon-Fuentes, C. del Pozo, *Org. Lett.* **2010**, *12*, 3484; h) S. Ye, J. Liu, J. Wu, *Chem. Commun.* **2012**, *48*, 5028.

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

[6] a) T. Xu, G. Liu, *Org. Lett.* **2012**, *14*, 5416; b) C. Si, A. G. Myers, *Angew. Chem.* **2011**, *123*, 10593; *Angew. Chem. Int. Ed.* **2011**, *50*, 10409.

[7] For selected examples, see: a) C. Chen, L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 12454; b) F. Baert, J. Colomb, T. Billard, *Angew. Chem.* **2012**, *124*, 10528; *Angew. Chem. Int. Ed.* **2012**, *51*, 10382; c) G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 7450; *Angew. Chem. Int. Ed.* **2011**, *50*, 7312; d) C.-P. Zhang, D. A. Vicic, *J. Am. Chem. Soc.* **2012**, *134*, 183; e) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan, K.-W. Huang, *Angew. Chem.* **2013**, *125*, 1588; *Angew. Chem. Int. Ed.* **2013**, *52*, 1548; f) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang, F.-L. Qing, *Angew. Chem.* **2012**, *124*, 2542; *Angew. Chem. Int. Ed.* **2012**, *51*, 2492; g) C.-P. Zhang, D. A. Vicic, *Chem. Asian J.* **2012**, *7*, 1756; h) X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem.* **2013**, *125*, 3541; *Angew. Chem. Int. Ed.* **2013**, *52*, 3457; i) L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 18240.

[8] a) A. Tlili, T. Billard, *Angew. Chem.* **2013**, *125*, 6952; *Angew. Chem. Int. Ed.* **2013**, *52*, 6818; b) Y. Yang, X. Jiang, F.-L. Qing, *J. Org. Chem.* **2012**, *77*, 7538; c) A. Ferry, T. Billard, E. Bacqué, B. R. Langlois, *J. Fluorine Chem.* **2012**, *134*, 160; d) A. Ferry, T. Billard, B. R. Langlois, E. Bacqué, *J. Org. Chem.* **2008**, *73*, 9362; e) A. Ferry, T. Billard, B. R. Langlois, E. Bacqué, *Angew. Chem.* **2009**, *121*, 8703; *Angew. Chem. Int. Ed.* **2009**, *48*, 8551; f) A. Ferry, T. Billard, B. R. Langlois, E. Bacqué, *J. Org. Chem.* **2008**, *73*, 9362; g) Q. Xiao, J. Sheng, Z. Chen, J. Wu, *Chem. Commun.* **2013**, *49*, 8647.

[9] For selected examples, see: a) H. Ren, Y. Luo, S. Ye, J. Wu, *Org. Lett.* **2011**, *13*, 2552; b) S. Ye, H. Wang, J. Wu, *ACS Comb. Sci.* **2011**, *13*, 120; c) Q. Xiao, S. Ye, J. Wu, *Org. Lett.* **2012**, *14*, 3430; d) D. Zheng, Z. Chen, J. Liu, J. Wu, *Org. Biomol. Chem.* **2011**, *9*, 4763; e) H.-S. Yeom, S. Kim, S. Shin, *Synlett* **2008**, 924; f) Z. Huo, H. Tomeba, Y. Yamamoto, *Tetrahedron Lett.* **2008**, *49*, 5531.

[10] a) J. H. Clark, C. W. Jones, A. P. Kybett, M. A. Mcclinton, J. M. Miller, D. Bishop, R. J. Blade, *J. Fluorine Chem.* **1990**, *48*, 249; b) G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 7450; *Angew. Chem. Int. Ed.* **2011**, *50*, 7312.

Received: September 14, 2013
Published Online: November 26, 2013

