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Generation of 1-(trifluoromethyl)-1,2-dihydroisoquinolines via a silver(I)-catalyzed reaction of 2-alkynylaryl aldimine with trimethyl(trifluoromethyl)silane

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ABSTRACT

A silver(I)-catalyzed reaction of 2-alkynylaryl aldimine with trimethyl(trifluoromethyl)silane is reported. This reaction proceeds efficiently under extremely mild conditions to generate 1-(trifluoromethyl)-1,2-dihydroisoquinolines in good yields. A three-component reaction of 2-alkynylbenzaldehyde, amine, with trimethyl(trifluoromethyl)silane is presented as well.

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Recently, the fluorine chemistry has attracted much attention due to the importance of fluorinated small molecules in medicinal chemistry, pharmaceuticals, and agricultural chemicals.[1] For example, more than 20% of commercial drugs contain fluorine. Currently, organic and medicinal chemists are focusing on the introduction of fluorine into drugs or leading compounds, with an expectation to significantly improve their medicinal properties.[2] As a part of program aiming at the incorporation of fluorine into natural product-like compounds with privileged scaffolds, we are interested in the synthesis of fluorinated isoquinolines and its related library.

The skeleton of isoquinoline core could be found in many natural products and pharmaceuticals.[3–5] The application of the fluorinated isoquinolines has been discovered as well. For instance, some biologically active compounds (including antiproliferative drug, myosin inhibitor, and agent for reducing intraocular pressure) have been designed and synthesized by using fluorinated isoquinolines as building blocks.[6] Thus, the development of efficient route to fluorinated isoquinolines is highly important.[7] Recently, Liu and co-workers described the synthesis of 4-fluoroisoquinolines **A** via a silver-catalyzed intramolecular oxidative aminofluorination of alkynes using NSFI as the fluorine source (Fig. 1).[7a] We also discovered that, in the presence of *p*-methoxybenzenesulfonyl chloride, 1-((trifluoromethyl)thio)isoquinolines **B** could be constructed through a silver(I)-catalyzed reaction of 2-alkynylbenzaldoxime with silver trifluoromethyl)thiolate.[7b] Prompted by these results and due to the importance of the trifluoromethyl group,[8] we conceived that the trifluoromethyl group could be introduced in the isoquinoline scaffold as well (compound **C**). We anticipated that the library of trifluoromethyl substituted isoquinolines would be beneficial for the subsequent biological evaluations.

Initially, we expected that 1-trifluoromethylisoquinolines could be generated via a silver(I)-catalyzed reaction of 2-alkynylbenzaldoxime with trifluoromethyl anion as well under the standard conditions we developed.[7b] However, the reaction failed after detailed investigations. Therefore, a model reaction of 2-alkynylbenzaldimine **1a** with trimethyl(trifluoromethyl)silane **2** was selected for reaction development. Since 2-alkynylbenzaldimine **1a** would

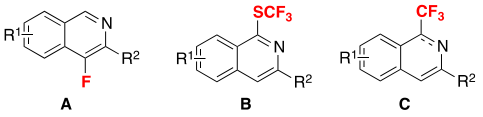

Figure 1. Fluorinated isoquinolines.

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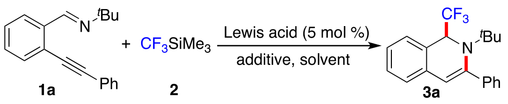
Table 1
Initial studies for the reaction of 2-alkynylbenzaldimine **1a** with trimethyl(trifluoromethyl)silane **2**



Entry	[M]	Solvent	Temp	Additive	Yield[a] (%)
1	Pd(OAc)$_2$	MeCN	80	–	7
2	Pd(TFA)$_2$	MeCN	80	–	10
3	AgOTf	MeCN	80	–	15
4	CuI	MeCN	80	–	Trace
5	CuSO$_4$	MeCN	80	–	nr
6	AgSbF$_6$	MeCN	80	–	31
7	AgBF$_4$	MeCN	80	–	19
8	AgTFA	MeCN	80	–	28
9	Bi(OTf)$_3$	MeCN	80	–	nr
10	AgSbF$_6$	MeCN	0	–	25
11	AgSbF$_6$	MeCN	25	–	47
12	AgSbF$_6$	MeCN	40	–	40
13	AgSbF$_6$	MeCN	60	–	23
14	AgSbF$_6$	MeCN	100	–	29
15	AgSbF$_6$	DCE	25	–	32
16	AgSbF$_6$	Toluene	25	–	19
17	AgSbF$_6$	DMSO	25	–	14
18	AgSbF$_6$	DMA	25	–	Trace
19	AgSbF$_6$	THF	25	–	26
20	AgSbF$_6$	Dioxane	25	–	Trace
21	AgSbF$_6$	DMF	25	–	38
22	AgSbF$_6$	MeCN	25	Cs$_2$CO$_3$	Trace
23	AgSbF$_6$	MeCN	25	DABCO	18
24	AgSbF$_6$	MeCN	25	NaOAc	53
25	AgSbF$_6$	MeCN	25	HOAc	88
26	AgSbF$_6$	MeCN	25	CF$_3$CO$_2$H	nd
27	AgSbF$_6$	MeCN	25	TsOH	nd
28	AgSbF$_6$	MeCN	25	PhCO$_2$H	73

[a] Isolated yield based 2-alkynylbenzaldimine **1a**.

undergo 6-*endo* cyclization in the presence of Lewis acid,[9] this would facilitate subsequent nucleophilic attack. Thus, different Lewis acids were evaluated in acetonitrile at 80 °C (Table 1). At the outset, the corresponding product **3a** was obtained and isolated in 7% yield when palladium acetate was used as the catalyst (Table 1, entry 1). A similar outcome was observed when Pd(TFA)$_2$ was utilized (Table 1, entry 2). A higher yield was obtained when silver(I) triflate was employed in the transformation (Table 1, entry 3). However, the reaction failed when copper salts were used (Table 1, entries 4 and 5). Interestingly, the desired 1-(trifluoromethyl)-1,2-dihydroisoquinoline **3a** was produced in 31% yield when the reaction was catalyzed by silver hexafluorostiboranuide (Table 1, entry 6). The result could not be improved when other silver salts were used as replacement (Table 1, entries 7 and 8). Further exploration of temperature revealed that the reaction worked efficiently at 25 °C, which afforded product **3a** in 47% yield

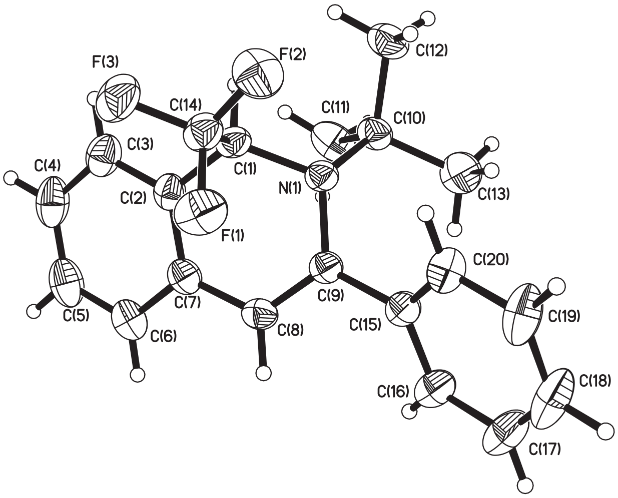
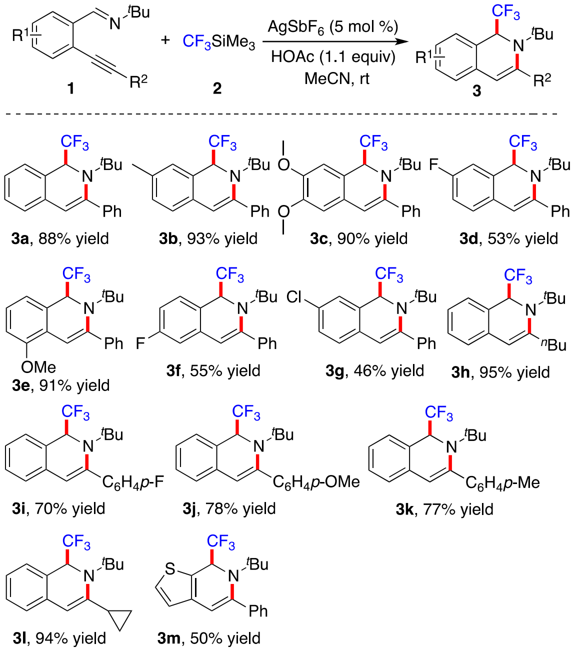
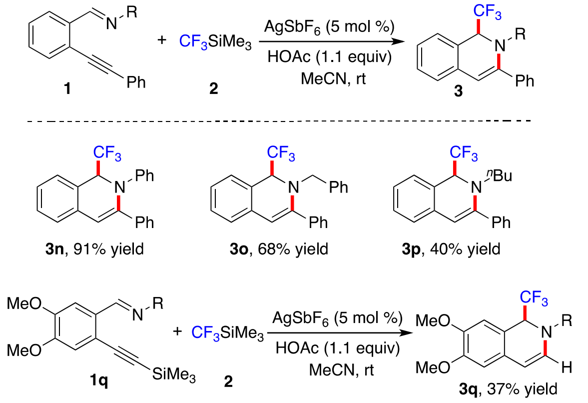


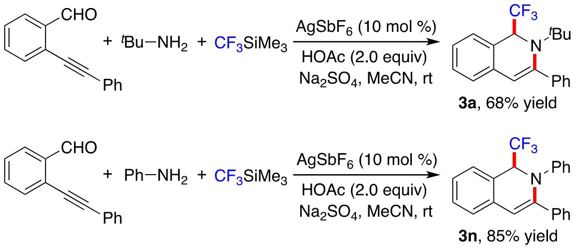
Figure 2. X-ray ORTEP illustration of compound **3a** (30% probability ellipsoids).



Scheme 1. Synthesis of 1-(trifluoromethyl)-1,2-dihydroisoquinolines **3** via a silver(I)-catalyzed reaction of 2-alkynylbenzaldimine **1** with trimethyl(trifluoromethyl)silane **2**.[a](Isolated yield based on 2-alkynylbenzaldimine **1**.)



Scheme 2. Silver(I)-catalyzed reaction of 2-alkynylbenzaldimine **1** with trimethyl(trifluoromethyl)silane **2**.[a](Isolated yield based on 2-alkynylbenzaldimine **1**.)



Scheme 3. A silver(I)-catalyzed three-component reaction of 2-alkynylbenzaldehyde, amine, with trimethyl(trifluoromethyl)silane.

(Table 1, entries 10–14). The survey of solvents discovered that acetonitrile was the best choice, and inferior yields were obtained when the reaction was performed in other solvents (Table 1, entries 15–21). With these results in hand, we considered to improve the nucleophilicity of trimethyl(trifluoromethyl)silane **2**. Therefore, different bases were screened (Table 1, entries 22–24). The desired product **3a** was obtained in 53% yield when NaOAc was added in the reaction. Further exploration revealed that the reaction proceeded efficiently in the presence of 1.1 equiv of HOAc, giving rise to the corresponding product **3a** in 88% yield. We reasoned that the presence of acetic acid might act a Brønsted acid for the activation of the imine group. In the meantime, the structure of 1-(trifluoromethyl)-1,2-dihydroisoquinoline **3a** was illustrated by X-ray analysis (Fig. 2).

Under the optimized conditions (5 mol % of $AgSbF_6$, 1.1 equiv of HOAc, MeCN, 25 °C), we then explored the generality of this transformation. The results are presented in Scheme 1. Various substituted 2-alkynylbenzaldimines **1** with trimethyl(trifluoromethyl) silane **2** were evaluated. It was found that reactions of 2-alkynylbenzaldimines **1** with electron-donating groups attached on the aromatic backbone afforded the expected products in excellent yields. However, moderate yields of 1-(trifluoromethyl)-1,2-dihydroisoquinolines **3** were obtained when 2-alkynylbenzaldimines **1** with electron-withdrawing groups attached on the aromatic ring were employed. For examples, the methoxy-substituted 1-(trifluoromethyl)-1,2-dihydroisoquinoline **3e** was isolated in 91% yield, while the chloro-substituted product **3g** was furnished in 46% yield. Additionally, 2-alkynylbenzaldimines **1** with different groups attached on triple bond could be compatible under the standard conditions. For instance, the cyclopropyl-substituted product **3l** was generated in 94% yield. Moreover, the thiophenyl-incorporated substrate worked efficiently as well, leading to the corresponding product **3m** in 50% yield.

Subsequently, we examined the reactions of trimethyl(trifluoromethyl)silane and 2-alkynylbenzaldimines with different groups attached on the nitrogen atom (Scheme 2). The reactions proceeded smoothly as expected. Not only the phenyl group but also alkyl groups (benzyl and *n*-butyl) were compatible under the optimized conditions. Interestingly, the desilyl product **3q** was obtained when 2-alkynylbenzaldimine with the trimethylsilyl group attached on the triple bond was employed in the reaction of trimethyl(trifluoromethyl)silane (Scheme 2).

Moreover, it was found that the expected 1-(trifluoromethyl)-1,2-dihydroisoquinolines **3** could be afforded via a silver(I)-catalyzed three-component reaction of 2-alkynylbenzaldehyde, amine, with trimethyl(trifluoromethyl)silane (Scheme 3). For instance, 2-alkynylbenzaldehyde reacted with *tert*-butyl amine and trimethyl (trifluoromethyl)silane leading to the corresponding product **3a** in 68% yield. When aniline was used as a replacement, the desired product **3n** was generated in 85% yield.

In conclusion, we have described a silver(I)-catalyzed reaction of 2-alkynylaryl aldimine with trimethyl(trifluoromethyl)silane for the synthesis of 1-(trifluoromethyl)-1,2-dihydroisoquinolines. This transformation proceeds efficiently under extremely mild conditions to generate the corresponding products in good yields. A three-component reaction of 2-alkynylbenzaldehyde, amine, with trimethyl(trifluoromethyl)silane is presented as well. The broad reaction scope is demonstrated and the diversity could be easily introduced.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.064. These data include MOL files and InChiKeys of the most important compounds described in this article.

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