บทความวิชาการ

ความก้าวหน้าของปฏิกิริยาไตรฟลูออโรเมทิลเลชันโดยใช้โลหะเงินเป็นตัวกลางหรือตัวเร่งปฏิกิริยา

นคินทร์ สุรพานิช*

บทคัดย่อ

สารอินทรีย์ที่มีหมู่ไตรฟลูออโรเมทิล (CF_3) เป็นองค์ประกอบจำนวนมากมีความสำคัญทางการแพทย์ ทางเกษตรกรรม และทางวัสดุศาสตร์ ด้วยเหตุนี้เองจึงเป็นแรงกระตุ้นทำให้มีการพัฒนาวิธีใหม่ๆ เพื่อที่จะสังเคราะห์สารอินทรีย์ที่มีหมู่ไตรฟลูออโรเมทิลเป็นองค์ประกอบ ในช่วงตลอดระยะเวลา 7 ปี ที่ผ่านมา พบว่าปฏิกิริยาไตรฟลูออโรเมทิลเลชันโดยใช้โลหะแทรนซิชันได้แก่ Pd และ Cu เป็นตัวกลางหรือตัวเร่งปฏิกิริยาได้รับความสนใจอย่างแพร่หลายเนื่องจากเป็นวิธีที่มีประสิทธิภาพในการสังเคราะห์สารอินทรีย์ที่มีหมู่ไตรฟลูออโรเมทิลเป็นองค์ประกอบ ในบทความนี้จะกล่าวถึงความก้าวหน้าของปฏิกิริยาไตรฟลูออโรเมทิลเลชันโดยใช้โลหะเงิน เป็นตัวกลางหรือตัวเร่งปฏิกิริยา ซึ่งผลจากการค้นพบนี้นำไปสู่โอกาสใหม่ๆ ที่จะประสบความสำเร็จในการสังเคราะห์สารอินทรีย์ที่มีหมู่ไตรฟลูออโรเมทิลเป็นองค์ประกอบได้อย่างหลากหลาย โดยใช้สารตั้งต้นที่ไม่เป็นอันตราย หาซื้อได้ง่ายราคาถูกและใช้สภาวะในการทำปฏิกิริยาที่ไม่รุนแรง ในบทความนี้ยังกล่าวถึงรายละเอียดของกลไกการเกิดปฏิกิริยาที่แสดงให้เห็นว่าโลหะเงินมีส่วนเกี่ยวข้องอย่างไรที่ทำให้ปฏิกิริยาไตรฟลูออโรเมทิลเลชันเกิดผลสัมฤทธิ์

คำสำคัญ: ออร์กาโนฟลูออรีน วิธีการสังเคราะห์ ปฏิกิริยาไตรฟลูออโรเมทิลเลชัน โลหะเงิน

สาขาวิชาเคมี คณะวิทยาศาสตร์และเทคโนโลยี มหาวิทยาลัยราชภัฏราชนครินทร์

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Progress in Silver-Mediated/Catalyzed Trifluoromethylation

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ABSTRACT

Many organic compounds containing trifluoromethyl group (CF_3) which are one of the most important classes of organic compounds are often finding applications as pharmaceuticals, agrochemicals, and materials. Therefore, the development of new methods for preparing trifluoromethylated compounds has been recently paid much attention. Over the past 7 years, a variety of Pd and Cu have been reported as a major achievement for transition-metal-mediated/catalyzed trifluoromethylation. In this context, we will discuss silver as transition-metal-mediated/catalyzed trifluoromethylation of organic molecules on both aromatic rings and aliphatic chains. The development of these silver-mediated/catalyzed trifluoromethylation could lead to new opportunities for synthesis of trifluoromethylated targets with ready availability of starting materials, low cost of the safe trifluoromethylating reagents, and mild experimental conditions. Moreover, the detailed reaction mechanisms of silver-mediated/catalyzed trifluoromethylations are also discussed.

Keywords: organofluorine, synthetic method, trifluoromethylation, silver

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Introduction

The unique properties of fluorine such as strong polar interactions and small size often affect the chemical, physical, and biological properties of the fluorinated molecules [1-5]. The incorporation of fluorine or fluorine containing groups into organic molecules has attracted much attention because many fluorinated compounds are finding applications as agrochemicals [6], pharmaceuticals [7, 8], tracers for positron emission tomography (PET) [9], and other valuable materials [10]. Trifluoromethylated compounds are one of the most important classes of organic compounds because trifluoromethyl group has unique size and special electronic properties which lead to major changes in lipophilicity of the parent molecule to promote penetration through cell membranes, enhancing binding selectivity of the bioactive molecules, and increasing metabolic stability. Accordingly, trifluoromethylated compounds play a key role in pharmaceuticals, agrochemicals, and materials. For instance, the anti-depression drug Prozac, the non-steroidal anti-inflammatory drug Celebrex, the oral non-steroidal anti-androgen drug Casodex, and the pesticide Fipronil are commercially available pharmaceuticals and agrochemicals [7, 8, 11, 12] (Figure 1).

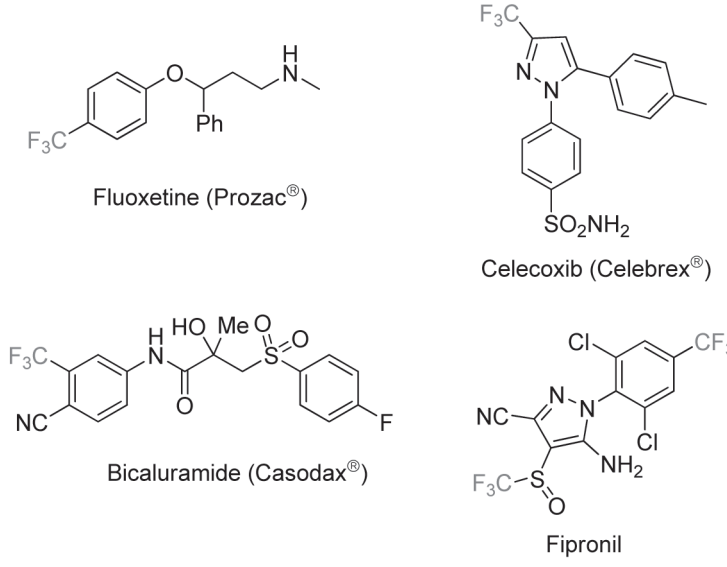
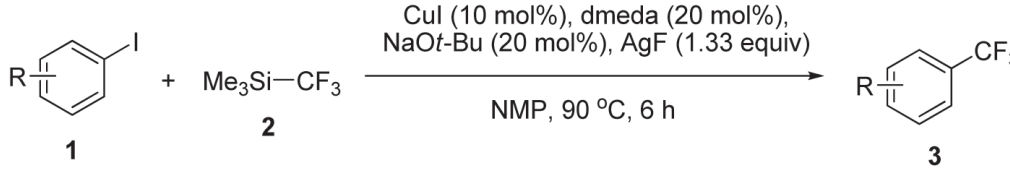
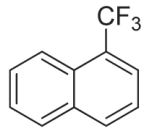


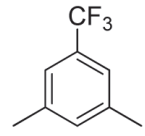
Figure 1 Some examples of pharmaceuticals and agrochemicals containing trifluoromethyl group

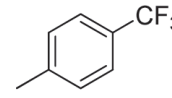
As a result, much effort has been paid to the development of new methods for introducing trifluoromethyl group (CF_3) into organic molecules. Over the past 7 years, a variety of Pd and Cu have been achieved in transition-metal-mediated/catalyzed trifluoromethylation of aryl halides, aryl boronic acids, and aromatic carbon-hydrogen bonds. Most of them, however, have had some limitation such as limited substrate scopes and required harsh reaction conditions. In addition, recently, rare but interesting examples of silver-mediated/catalyzed trifluoromethylation have been reported as a promising strategy and solution. In 2011, Weng and co-workers [13] reported an effective model of cooperative effect of silver for copper-catalyzed trifluoromethylation of activated and unactivated aryl iodides 1 to trifluoromethylated arenes. The reaction conditions employed (trifluoromethyl)trimethylsilane (2) (Me_3SiCF_3, "Ruppert-Prakash reagent") as trifluoromethyl source. Under the optimized reaction conditions using 1.0 equiv of aryl iodide and 2.0 equiv of Me_3SiCF_3 in the presence of 10 mol% of CuI, 20 mol% of *N,N'*-dimethylethylenediamine (dmeda), 20 mol% of NaO*t*-Bu, and 1.35 equiv of AgF in *N*-methylpyrrolidone (NMP) at 90°C for 6 hours, trifluoromethylation of aryl iodide was achieved with a broad substrate scope (Table 1).

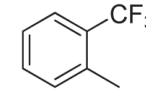
Table 1 Cooperative effect of silver in copper-catalyzed trifluoromethylation of aryl iodides

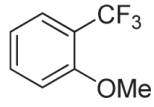


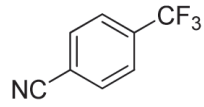

3a, 75%[a]

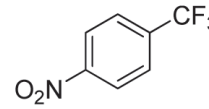

3b, 76%[a]

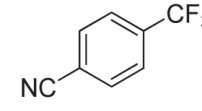

3c, 73%[b]


3d, 59%[b]


3e, 66%[b]

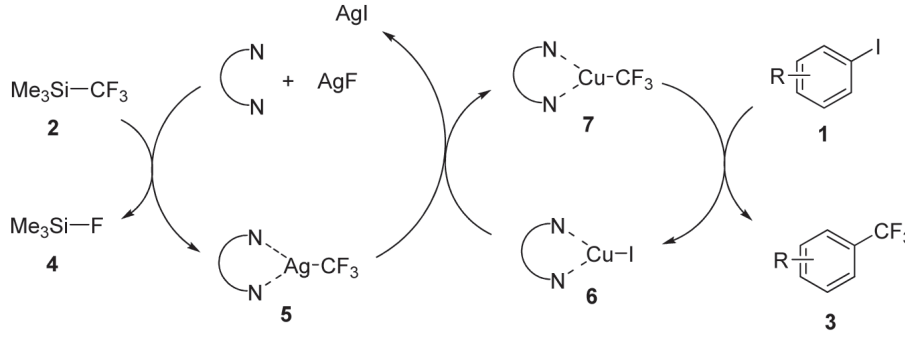

3f, 89%[b]


3g, 98%[a]


3h, 89%[b]

[a] Isolated yield. [b] Determined by ^{19}F NMR.

As shown in Scheme 1, the reaction pathway of Cu/Ag-catalyzed trifluoromethylation of aryl iodides was proposed. The trifluoromethyl silver bond **5** was first generated. The transmetalation of the trifluoromethyl silver species **5** with copper iodide formed the trifluoromethyl copper species **7** which was reacted with iodoarenes **1** releasing the trifluoromethylated arenes **3** and regenerated copper iodide **6** as a catalyst.



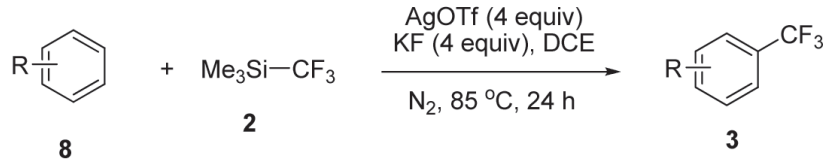
Scheme 1 Proposed reaction mechanism for the Cu/Ag-catalyzed trifluoromethylation

In contrast to both recent Cu- and Pd-catalyzed trifluoromethylation of aryl halides [29, 30], the silver-assisted copper-catalyzed trifluoromethylation uses a commercially available Me_3SiCF_3 as trifluoromethyl source. The Me_3SiCF_3 is not a suitable trifluoromethylating reagent in the Cu- and Pd-catalyzed trifluoromethylation reaction probably due to trifluoromethyl anion (CF_3^-) generated more quickly and its self-decomposition in the presence of fluoride in the reactions. In order to overcome this drawback, Weng and co-workers use silver (I) to stabilize the unstable trifluoromethyl anion (CF_3^-) to form silver species **5** which facilitate transmetallation in the next step. The advantages of this transformation include ready availability and low cost of the safe trifluoromethylating reagent (Me_3SiCF_3), and the wide functional group compatibility.

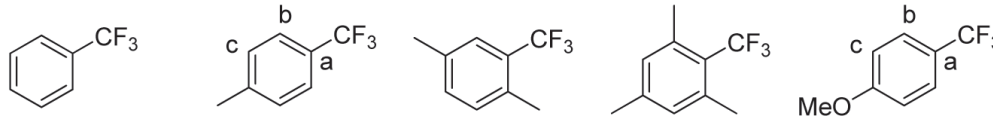
C-H Bond trifluoromethylation methods are particularly attractive because they do not require prefunctionalized starting materials. Over the past 5 years, a handful of Pd and Cu-based protocols have been reported for trifluoromethylation of C-H bond [31, 32]. These reactions have significant limitations. Some systems use directing group strategy and expensive trifluoromethylating reagents. Others require temperature greater than 100°C. All of them remain especially limited in substrate scope. To identify metals other than Cu or Pd that could promote trifluoromethylation of C-H bond. In 2011, Sanford and co-workers [14] developed silver-mediated C-H trifluoromethylation of aromatic substrates **3** using a combination of AgOTf, KF, and Me_3SiCF_3 (**2**) as trifluoromethyl source. In general, the silver-mediated C-H

trifluoromethylation proceeded with a modest yield preference at *ortho* and *para* position to the electro-donating alkyl or alkoxy groups. Heteroaromatics such as *N*-methyl pyrrole, thiophene, and caffeine were also converted to corresponding trifluoromethylated products **9, 10** and **11** in moderate to good yields under the reaction conditions (Table 2). However, the scope and synthetic application of the reaction is limited, because an excess of the aromatic substrate is needed and only iodo-, methyl-, and methoxy-substituted aromatic substrates are shown to be compatible with the reaction conditions.

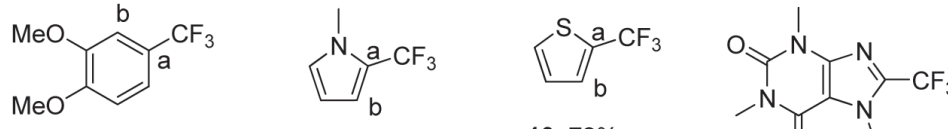
Table 2 Silver-mediated trifluoromethylation of arenes[a,b]



8 **2** **3**



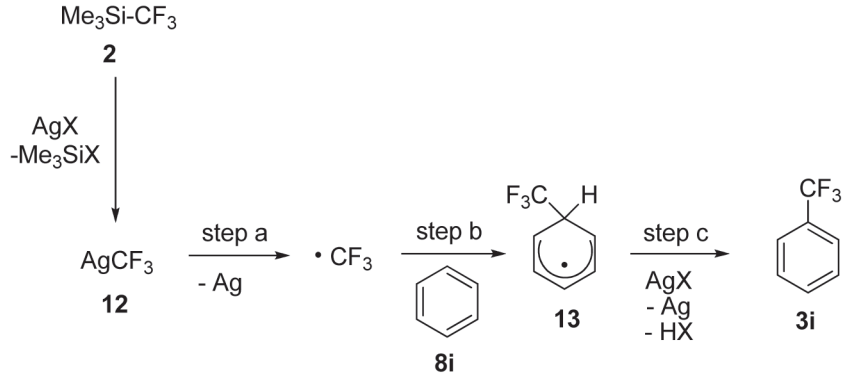
3i, 87% **3j**, 81% isomer ratio (a : b : c) (2.7 : 1.4 : 1) **3k**, 76% **3l**, 78% **3m**, 87% isomer ratio (a : b : c) (1.2 : 1 : 2.7)



3n, 70% isomer ratio (a : b) (4 : 1) **9**,[c] 44% isomer ratio (a : b) (20 : 1) **10**, 72% isomer ratio (a : b) (8 : 1) **11**,[d] 42%

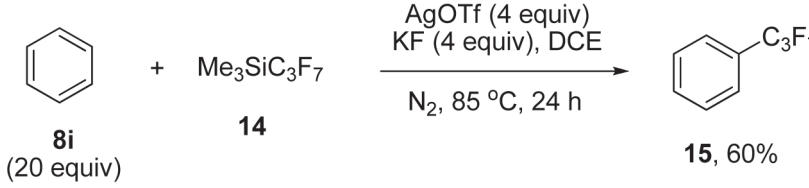
[a] General conditions: substrate (10 equiv), $TMSCF_3$ (1 equiv) in dichloroethane (DCE) at 85 °C for 24 h. [b] Yield and selectivity determined by ^{19}F NMR analysis of the crude reaction mixture. [c] 20 equiv of substrate was used. [d] 5 equiv of substrate was used.

The reaction mechanism of the silver-mediated C-H trifluoromethylation was proposed as shown in Scheme 2. The trifluoromethyl silver species **12** was first generated by the reaction of silver halide with Me_3SiCF_3 (**2**). Ag(I) acting as an oxidant produced a trifluoromethyl radical (•CF_3) (Scheme 2, step a) which then underwent a radical aromatic substitution reaction affording intermediate **13** (step b). Subsequent single electron transfer (SET) from intermediate **13** to a second equivalent of Ag(I) would release the trifluoromethylated arenes 3 along with HOTf and Ag (step c).



Scheme 2 Possible free radical mechanism for Ag-mediated trifluoromethylation

Moreover, the reaction of this silver-mediated trifluoromethylation could be applied for transfer of other perfluoroalkyl groups to aromatic substrates (Scheme 3). Under the optimal conditions, the reaction of benzene **8i** with $Me_3SiC_3F_7$ (**14**) afforded (heptafluoropropyl)benzene (**15**) in 60% yield.

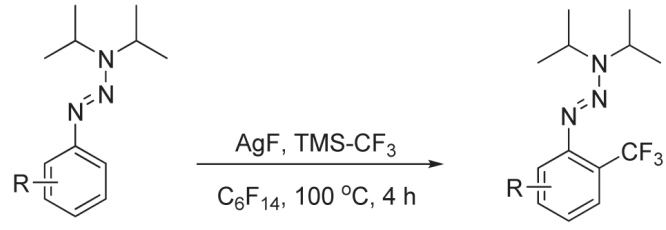


Scheme 3 Ag-mediated perfluoroalkylation of benzene

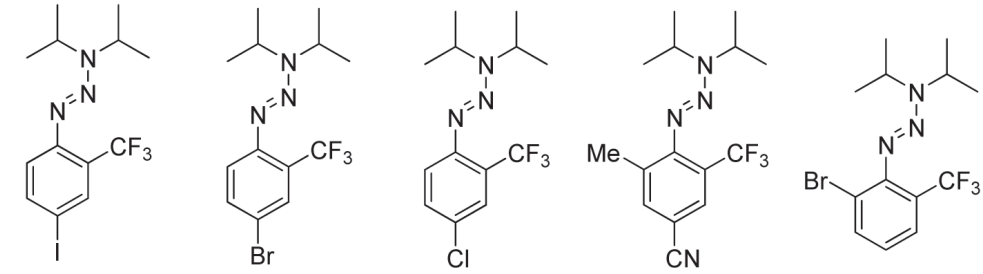
In 2012, independently from the Sanford's work, Bräse and co-workers [15] reported silver-mediated C-H trifluoromethylation of aromatic triazenes **16** using a combination of AgF, and Me_3SiCF_3 as trifluoromethyl source in C_6F_{14} as solvent at 100°C. Under the optimal conditions, the corresponding *o*-trifluoromethylated triazenes **17** were obtained in moderate yields (Table 3).

Notably, triazenes have been reported as a functional group equivalent of protected diazonium salts. Therefore, triazene compounds can be easily transformed into various functional groups which have been already reported in literatures [16-24]. To demonstrate this hypothesis, the *o*-trifluoromethylated triazenes **17** were transformed to the corresponding iodide **19a** [16, 17] and azide **18h** [18] under conventional conditions in good to excellent yields (Scheme 4).

Table 3 *Ortho*-trifluoromethylation of functionalized aromatic triazenes[a]



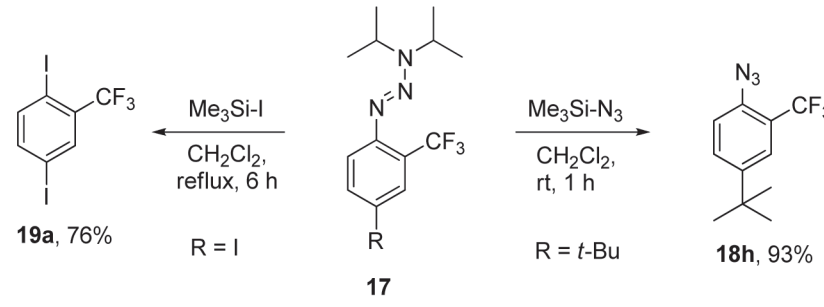
16 **17**



17a, 64% **17b**, 65% **17c**, 59% **17d**, 74% **17e**, 56%

17f, 39% **17g**, 51% **17h**, 56% **17i**, 53%

[a] Isolated yield.



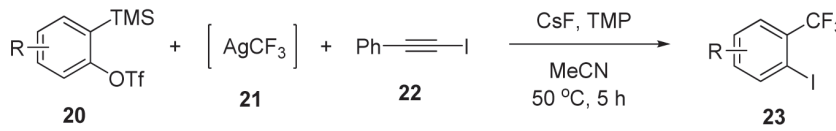
Scheme 4 Transformation of an *ortho*-trifluoromethylated triazene into the corresponding iodide **19a** and azide **18h**.

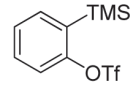
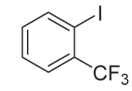
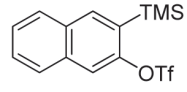
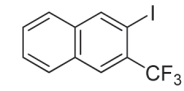
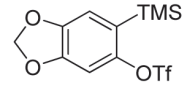
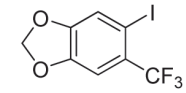
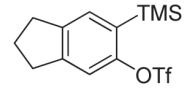
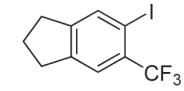
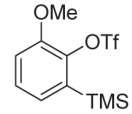
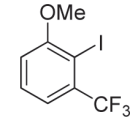
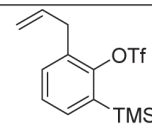
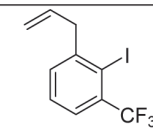
In the case of mechanistic investigation, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (5 equiv) known as a scavenger of CF_3 radicals was added to the reaction conditions. No corresponding product **17** could be obtained at all. The result confirms that the $\bullet CF_3$ radical intermediate should be involved in the reaction mechanism.

In contrast to the Sanford's work, this method employs directing group strategy to dictate trifluoromethylation of aromatic triazene at the position *ortho* to directing group giving high regioselectivity. However, some limitations of this reaction are observed such as prefunctionalized of starting materials, requirement for blocking groups to prevent *ortho,ortho'* -ditrifluoromethylation, and low yields of the corresponding *o*-trifluoromethylated triazenes.

Recently, an unprecedented silver-mediated vicinal trifluoromethylation-iodination of arynes has been developed by Hu and co-workers [25]. Under the optimized reaction conditions using a mixture of 1.0 equiv of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**20**), and 3.0 equiv of iodophenylacetylene (**22**) in the presence of 3.0 equiv of a freshly prepared $AgCF_3$ (**21**), 4.0 equiv of CsF, and 3.0 equiv of 2,2,6,6-tetramethylpiperidine (TMP) in MeCN, the iodotrifluoromethylbenzene products (**23**) were obtained in moderate to good yields (Table 4). This method provides a simple and efficient route to introduce CF_3 and I groups onto aromatic rings in a single step.

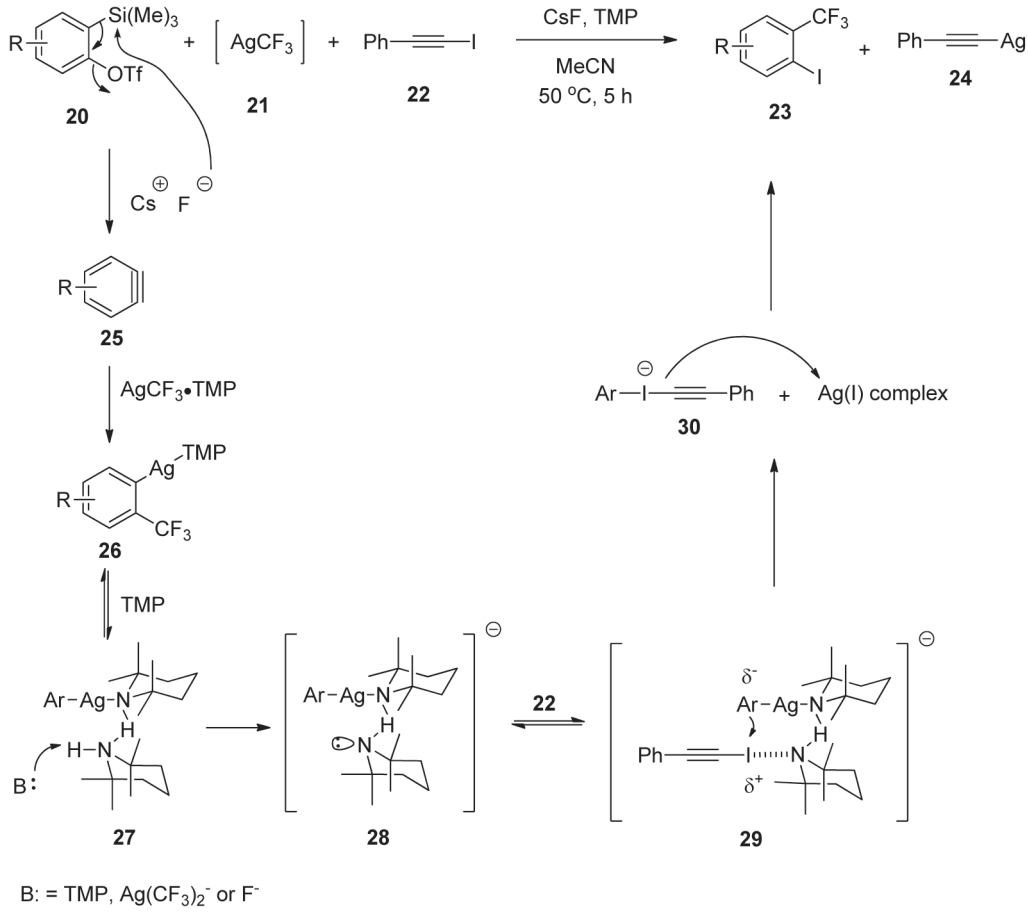
Table 4 Scope Of silver-mediated trifluoromethyl-iodination of arynes[a]



Entry	Substrates	Product	Yield (%)[b]
1	 **20a**	 **23a**	71
2	 **20b**	 **23b**	73
3	 **20c**	 **23c**	86
4	 **20d**	 **23d**	43
5	 **20e**	 **23e**	37
6	 **20f**	 **23f**	53

[a] Reaction conditions: **20** (0.1 mmol), **21** (freshly prepared, 0.3 mmol), **22** (0.3 mmol), CsF (0.4 mmol), and TMP (0.3 mmol) in MeCN (4 mL). [b] Isolated yields.

A plausible reaction mechanism for the silver-mediated trifluoromethylation-iodination process was proposed via the in situ-generated aryne **25** which was reacted with $AgCF_3$•TMP to give intermediate **26**. Intermediate **27** was formed by forming hydrogen bonds with another TMP and then underwent deprotonation to give anionic intermediate **28**, which can be stabilized by charge delocalization. Subsequent coordination of intermediate **28** with iodophenylacetylene via halogen bonding provided intermediate **29** followed by intramolecular nucleophilic attack to generate ate complex **30**. The complex **30** provided substituted *o*-iodotrifluoromethylbenzene **23** along with silver phenylacetylide (**24**) as a byproduct (Scheme 5).



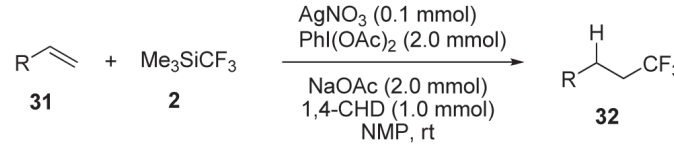
Scheme 5 A plausible reaction mechanism for the silver-mediated trifluoromethylation-iodination process

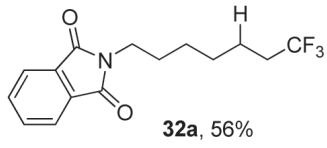
The first example of silver-catalyzed hydrotrifluoromethylation of unactivated alkenes **31** with Me_3SiCF_3 **(2)** as trifluoromethyl source and $PhI(OAc)_2$ as the oxidant has recently developed by Qing and co-workers [26]. The important key of the reaction is the use of a silver(I) salt and 1,4-cyclohexadiene (1,4-CHD) as H donor to inhibit the competitive deprotonative trifluoromethylation reaction. This method provides a wide range of trifluoromethylated products **32**, which have a wide range of functional groups tolerated, (Table 5).

According to the experimental results, the reaction pathway was believed by the generation of the CF_3 radical from Me_3SiCF_3 under oxidation conditions using $PhI(OAc)_2$ and catalytic amount of silver(I) salt. The radical species **33** was formed from the addition of the CF_3 radical to the alkene substrates **31**. The radical species **33** might undergo dismutation to give the corresponding alkanes **32** and alkenes (**34** and **35**) (Scheme 6, path b). In order

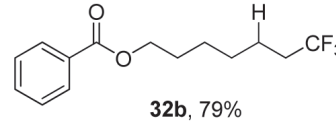
to suppress the undesired byproducts **34** and **35**, 1,4-cyclohexadiene (1,4-CHD) was employed as H donor to facilitate the H-abstraction process to give the corresponding alkanes **32** as a major product (Scheme 6, path a).

Table 5 Silver-catalyzed hydrotrifluoromethylation of alkenes with Me_3SiCF_3 [a]

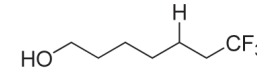




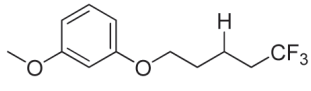
32a, 56%



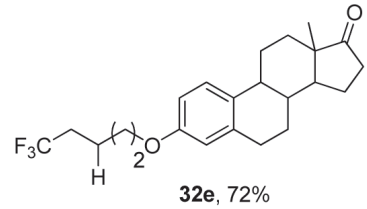
32b, 79%



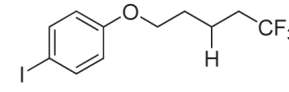
32c, 82%



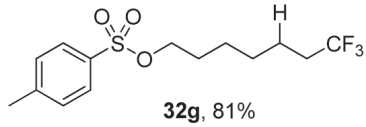
32d, 71%



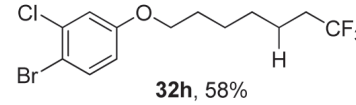
32e, 72%



32f, 78%

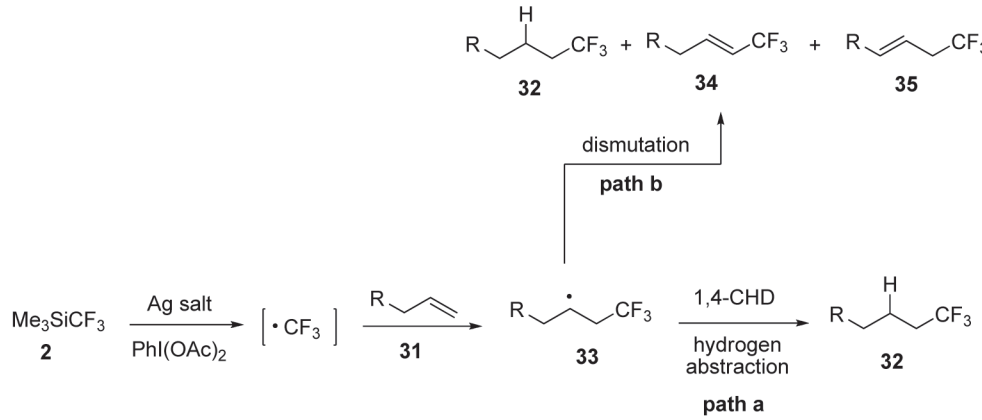


32g, 81%



32h, 58%

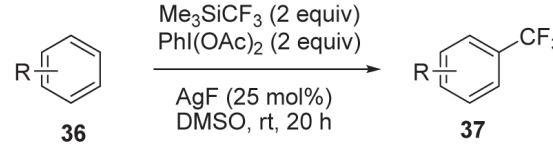
[a] Reaction conditions: **31** (1.0 mmol), Me_3SiCF_3 (4.0 mmol), $PhI(OAc)_2$ (2.0 mmol), NaOAc (2.0 mmol), $AgNO_3$ (0.1 mmol), 1,4-CHD (1.0 mmol), NMP (3 mL), rt, N_2 atmosphere, and a second portion of Me_3SiCF_3 (4.0 mmol),), $PhI(OAc)_2$ (2.0 mmol), NaOAc (2.0 mmol), 1,4-CHD (1.0 mmol), was added after 4 h.

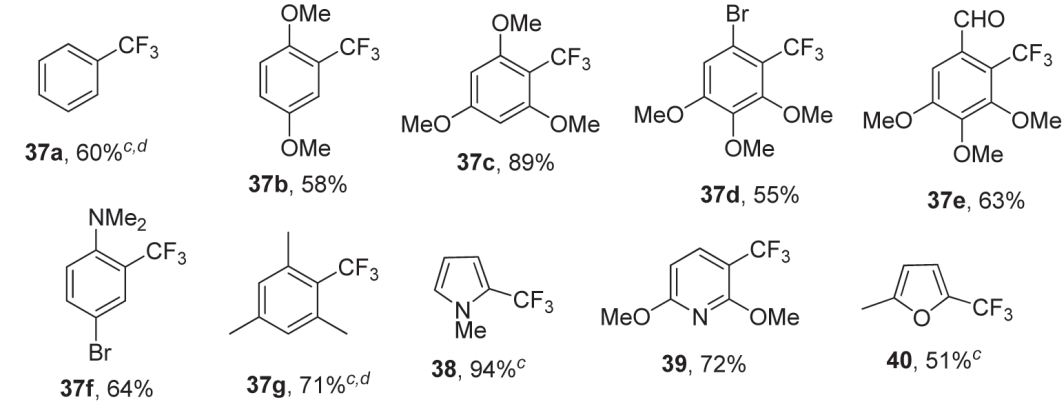


Scheme 6 A plausible reaction mechanism for the silver-catalyzed hydrotrifluoromethylation of unactivated alkenes **31** with Me_3SiCF_3 (**2**)

In 2013, Greaney and co-workers [27] reported a silver-catalyzed trifluoromethylation of arenes. The advantage of this reaction is operationally simple at room temperature under air and does not require excessive amount of substrate or reagent. A variety of heteroarenes and electron rich arenes can be converted to corresponding trifluoromethylated compounds **37** in moderate to good yields at room temperature with Me_3SiCF_3, catalytic silver, and $PhI(OAc)_2$ (Table 6).

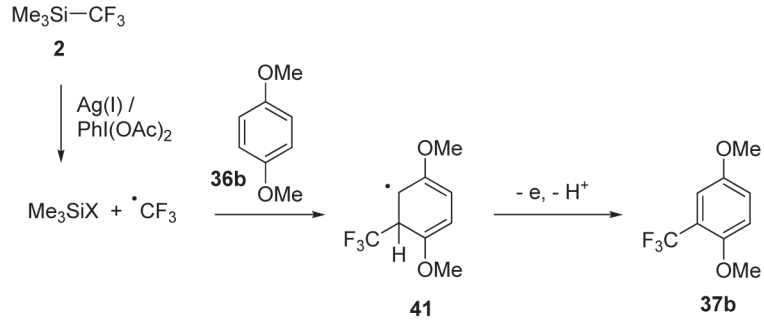
Table 6 Silver-catalyzed trifluoromethylation of arenes[a,b]





[a] Reaction conditions: **36** (0.3 mmol), Me_3SiCF_3 (0.6 mmol), $PhI(OAc)_2$ (0.6 mmol), and AgF (0.075 mmol) in DMSO (1.0 mL) at room temperature for 20 h. [b] Isolated yield. [c] Yield determined by ^{19}F NMR using 4-fluoroanisole as the internal standard. [d] Reaction conducted at 70 °C, 5-10 equiv of arene.

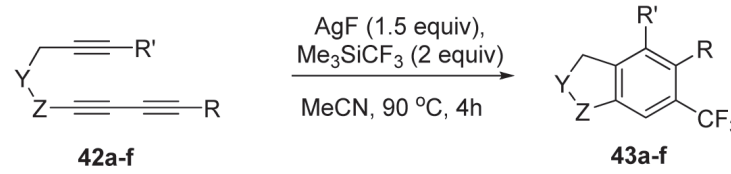
On the basis of mechanistic investigation, a possible reaction mechanism is shown in Scheme 7. The Me_3SiCF_3 (**2**) is oxidized by $PhI(OAc)_2$ and Ag(I) to generate CF_3 radical. Addition of CF_3 radical to aromatic ring to give intermediate **41** followed by a second one electron oxidation and proton loss to give the corresponding product **37b** (Scheme 7).



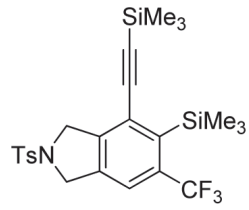
Scheme 7 A possible reaction mechanism of silver-catalyzed trifluoromethylation of arenes

In 2013, Lee and co-workers [28] reported a new approach of silver-mediated trifluoromethylation of arynes. It is a non-traditional synthesis of trifluoromethylated arenes from non-aromatic building blocks via thermal hexadehydro Diels-Alder reaction of bis-1, 3-diynes **42** and subsequent trapping of the resulting aryne intermediate with Me_3SiCF_3 as trifluoromethyl nucleophile. Under the optimal conditions, the corresponding trifluoromethylated arenes were obtained in good yield with high regioselectivity (Table 7).

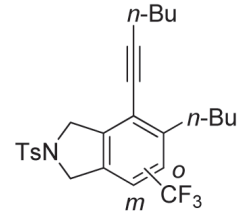
Table 7 Silver-mediated trifluoromethylation of arynes[a,b]



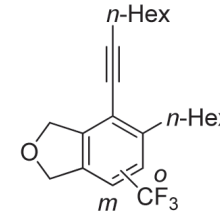
42a-f **43a-f**



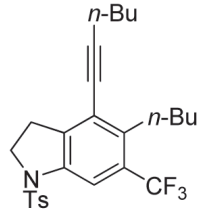
43a, 0%



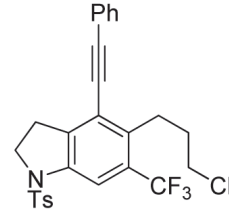
43b, 76%(*o*:*m* = 3:2)



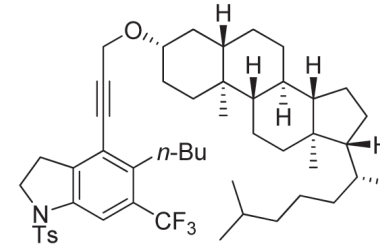
43c, 76% (*o*:*m* = 1:1)



43d, 75%



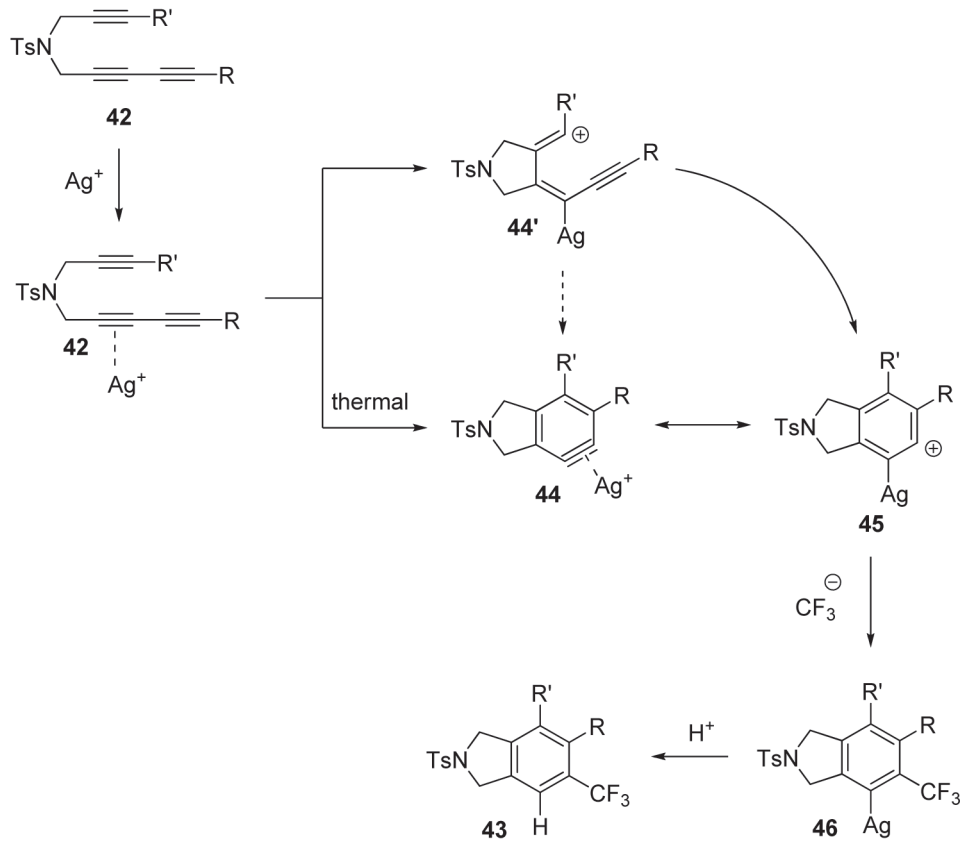
43e, 75%



43f, 67%

[a] Reaction conditions: **42** (1 equiv), AgF (1.5 equiv), Me_3SiCF_3 (2 equiv), in MeCN at 90 °C for 4 h. [b] Isolated yield.

The reaction mechanism of this silver-mediated trifluoromethylation of arynes is proposed via the concerted thermal hexadehydro-Diels-Alder reaction which is activated by silver-coordinated bis-1,3-diyne **42** followed by silver complexation to form intermediates **44** or **45**. Alternatively, the pathway involving silver-coordinated bis-1,3-diyne **42** and vinyl cation **44'**cannot be excluded because they lead to the key intermediates **44** and **45.** In the following steps, the addition of trifluoromethyl nucleophile onto electrophilic intermediate **45** will generate organosilver species **46.** Subsequent protonolysis of organosilver species **46** would release the corresponding trifluoromethylated arenes **43** (Scheme 8). According to The reaction mechanism of this silver-mediated trifluoromethylation, the organosilver species **46** was proposed. If it exists, the further fictionalizations by trapping with appropriate electrophile could be possible as seen in the reaction of silver-mediated trifluoromethyl-iodination of arynes (Scheme 5).



Scheme 8 The proposed reaction mechanism of this silver-mediate trifluoromethylation of arynes

Conclusion

The progress in silver-mediated/catalyzed trifluoromethylation developed during the past five years have shown significant advantages of incorporation of trifluoromethyl group into organic molecules on both aromatic rings and aliphatic chains. The advantages of the trifluoromethylation reactions include the ease of starting material preparation, the use of the ready availability and low cost of the safe trifluoromethylating reagents, the wide functional group compatibility, and the mild experimental conditions. Furthermore, the developed methods of the silver-mediated/catalyzed trifluoromethylation were applied for introducing trifluoromethyl group into complex molecules such as available bioactive compounds. The mechanisms of silver-mediated/catalyzed trifluoromethylation reactions were investigated and proved that the silver-mediated/catalyzed trifluoromethylation reactions are distinct from the conventional trifluoromethylation reactions. For instance, the effective trifluoromethylation was achieved by cooperative effect of silver in copper-catalyzed reaction, and the combination silver(I) and $PhI(OAc)_2$ promoted their oxidizing power to generate CF_3 radical which is

successful trifluoromethylation of both aromatics and aliphatic alkenes. The new reactivity of organosilver would trigger further development of silver-mediated/catalyzed trifluoromethylation as a tool for synthesis of fluorinated organic compounds. It is possible finding many useful applications in the fields of drug discovery, pharmaceutical synthesis, and material science.

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