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Silver-Mediated *N*-Trifluoromethylation of Sulfoximines

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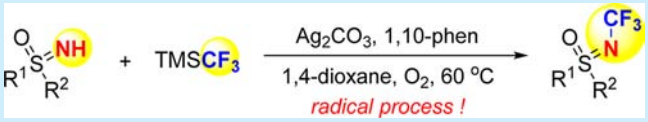
Supporting Information

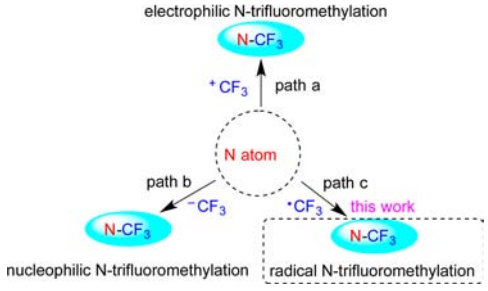
ABSTRACT: An unprecedented approach to *N*-trifluoromethylations of electron-rich nucleophilic sites following a radical pathway is reported. Accordingly, various sulfoximines (19 examples) have been *N*-trifluoromethylated, providing previously unreported products with satisfying functionality tolerance in moderate to good yields. With a C−N bond length at the N−CF_3 moiety of 1.341 Å the respective linkage is shorter than a traditional C−N single bond and comparable with that of a C−N double bond.



The incorporation of a trifluoromethyl group into an organic compound can significantly alter the properties of the molecule related to, for example, lipophilicity, metabolic stability, and conformational behavior.[1] In sharp contrast to the well-developed *C*-trifluoromethylations,[2] the formation of N−CF_3 bonds is still challenging, commonly involving a critical use of toxic reagents to be applied under harsh reaction conditions.[3] Undoubtedly, a direct *N*-trifluoromethylation with a commercially available, harmless trifluoromethylating agent would be highly desirable.[4]

For direct electrophilic *N*-trifluoromethylations (with the nitrogen atom being a hard nucleophile), only a few methods are known (Scheme 1, path a). Those include, for example, the approach by Umemoto, who applied in situ generated CF_3 cations for trifluoromethylations of amines.[5] In addition, Togni's *N*-trifluoromethylations of nitriles[6] and azoles[7] with hypervalent iodine reagents belong to this category. Alternatively, *N*-trifluoromethylation reactions could be envisioned proceeding via nucleophilic (Scheme 1, path b)[8] or radical pathways (Scheme 1, path c). Here, we exemplify the latter approach and report on an unprecedented silver catalysis allowing *N*-trifluoromethylations of sulfoximines leading to previously inaccessible products.

Scheme 1. Potential Pathways for Direct *N*-Trifluoromethylations



Sulfoximines have been applied in asymmetric synthesis[9] and directed C−H functionalizations.[10] Furthermore, some derivatives exhibit interesting bioactivities.[11] In all cases, fluorinated sulfoximines have attracted particular attention.[12]

For our search of a new *N*-trifluoromethylation method, we chose a combination of *S*,*S*-diphenylsulfoximine (**1l**) as a representative model substrate and Me_3SiCF_3 as trifluoromethylation agent. While both compounds did not react in the absence of a metallic activator (Table 1, entry 1), a smooth coupling occurred when the reagents were treated with a mixture of AgOAc (0.2 equiv) and 1,10-phenanthroline (**L1**, 0.4 equiv) in 1,4-dioxane at 50 °C under dioxygen. As a result, *N*-trifluoromethyl sulfoximine **2l** was obtained in 43% yield (Table 1, entry 2). Substituting AgOAc by AgCl did not lead to **2l** (Table 1, entry 3). When Ag_2O or AgF was applied as metallic catalyst component the yield of **2l** increased to 60% and 63%, respectively (Table 1, entries 4 and 5). The highest yield of **2l** (71%) was observed with Ag_2CO_3 (Table 1, entry 6). Varying the reaction temperature in catalyzes with this silver salt showed that 60 °C was better than 50 or 100 °C, allowing us to isolate **2l** in 85% yield (Table 1, entry 6). Using air or dinitrogen instead of dioxgyen affected the yield of **2l** negatively (Table 1, entry 6). Until then, only phenanthroline (**L1**) had been applied as ligand. Substituting **L1** in reactions with Ag_2CO_3 by DABCO (**L2**), neocuproine (**L3**), or 2,2′-bipyridine (**L4**) led to catalytically inactive systems (Table 1, entries 7−9). The essential role of **L1** was also revealed in an experiment performed in the absence of the ligand, which showed no product formation (Table 1, entry 10). Testing solvents other than 1,4-dioxane (Table 1, entries 11−14) proved the superiority of the latter. Attempts to decrease the catalyst loading remained unsuccessful, and the formation of a silver mirror or a black precipitate was observed.

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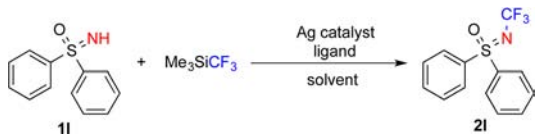
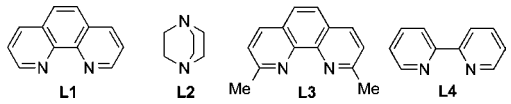
Table 1. Opimization of the Reaction Conditions[a]



entry	catalyst	ligand	solvent	yield (%)
1		**L1**	1,4-dioxane	<1
2	AgOAc	**L1**	1,4-dioxane	43
3	AgCl	**L1**	1,4-dioxane	<1
4	Ag_2O	**L1**	1,4-dioxane	60
5	AgF	**L1**	1,4-dioxane	63
6	Ag_2CO_3	**L1**	1,4-dioxane	71 (67),[b] (85),[c] (29),[d] (<1)[e]
7	Ag_2CO_3	**L2**	1,4-dioxane	<1
8	Ag_2CO_3	**L3**	1,4-dioxane	<5
9	Ag_2CO_3	**L4**	1,4-dioxane	<1
10	Ag_2CO_3		1,4-dioxane	<1
11	Ag_2CO_3	**L1**	DCE	11
12	Ag_2CO_3	**L1**	MeCN	8
13	Ag_2CO_3	**L1**	THF	<5
14	Ag_2CO_3	**L1**	toluene	<1

[a]Reaction conditions: sulfoximine **1l** (0.1 mmol), Me_3SiCF_3 (0.5 mmol), catalyst (0.02 mmol), ligand (0.04 mmol), and solvent (2.0 mL) at 50 °C under O_2 for 12 h, sealed tube. [b]100 °C. [c]60 °C. [d]Under air. [e]Under N_2.



The molecular structure of **2l** in the solid state was confirmed by X-ray crystal structure analysis (Figure 1).[13] Interestingly,

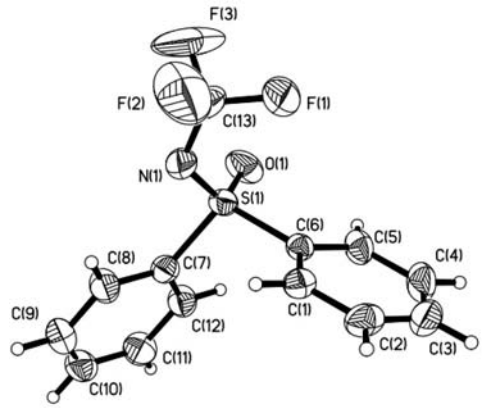


Figure 1. X-ray crystal structure (ORTEP) of product **2l**.

the length of the newly formed C−N bond was only 1.341 Å, which was significantly shorter than a traditional C−N single bond but compared well to the bond length of a C−N double bond.[14]

Next, the substrate scope and the limitations of the catalyzed coupling were investigated (Figure 2). Pleasingly, the functional group tolerance was high, and a wide range of products was accessible. In couplings of *S*-aryl-*S*-methyl sulfoximines, the respective products (**2a−i**) were obtained in yields ranging from 51% (for **2h**) to 78% (for **2c**). Stereoelectronic effects appeared to be of minor relevance. Alternations of the *S*-alkyl substituent (from methyl to butyl and cyclohexyl) had no significant impact on the product yields as revealed by

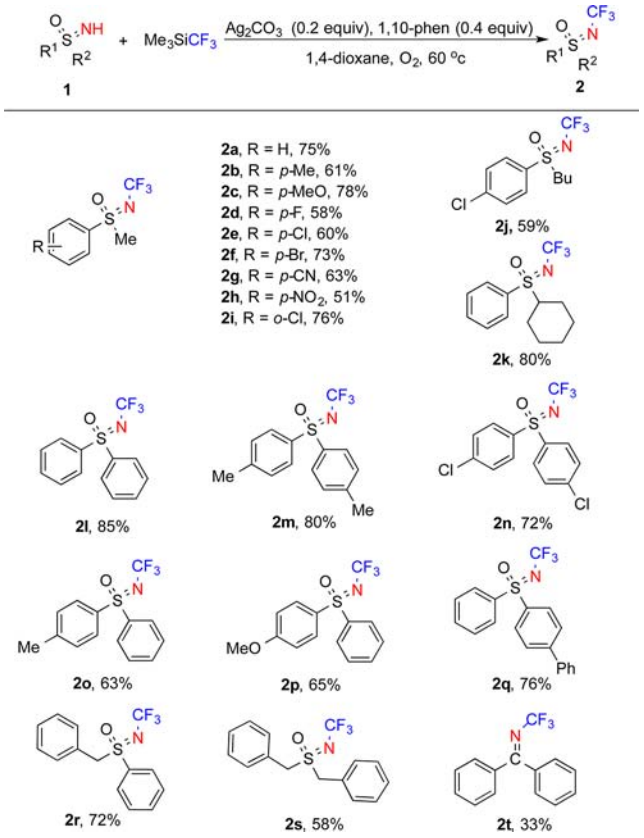


Figure 2. Substrate scope. Reaction conditions: sulfoximine (0.1 mmol), Me_3SiCF_3 (0.5 mmol), Ag_2CO_3 (0.02 mmol), 1,10-phen (0.04 mmol), and 1,4-dioxane (2.0 mL) at 60 °C under O_2 for 12 h in a sealed tube.

comparing the data for **2e** and **2j** (60% versus 59%) as well as **2a** and **2k** (75% versus 80%). In the series of *S*,*S*-diaryl sulfoximines, the yields of the corresponding products (**2l−q**) ranged from 63% (for **2o**) to 85% (for **2l**). Again, electronic effects were irrelevant. Considering the substitution pattern of various bioactive substrates,[11] the *N*-trifluoromethylations of *S*-benzyl-substituted sulfoximines **1r** and **1s** were of particular interest. Pleasingly, good results were obtained in both cases with yields of 72% and 58% for the corresponding products **2r** and **2s**, respectively. Finally, the conversion of benzophenone imine was attempted, and to our delight, the corresponding *N*-trifluoromethyl derivative **2t** was obtained in 33% yield.[15]

To demonstrate the practicality of the newly developed method, a 2 mmol scale reaction with **1l** as substrate was conducted, leading to the formation of **2l** in 73% yield.

To gain a better understanding of the reaction principles, selected mechanistic studies were conducted. Adding the radical scavengers TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) or galvinoxyl free radical [2,6-di-*tert*-butyl-α-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-*p*-tolyloxy] inhibited the reaction, and the corresponding CF_3 adducts **3** and **4** were detected by GC−MS (Scheme 2). Consequently, we presume trifluoromethyl radicals to be relevant intermediates, which in this case have been trapped by the radical scavengers.

Further studies with TEMPO (Table 2) revealed that both Ag_2CO_3 and 1,10-phenanthroline were essential for the in situ formation of the trifluoromethyl radical. If one of the reagents was missing, CF_3 addition product **3** could not be found.

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Scheme 2. Radical-Trapping Experiments

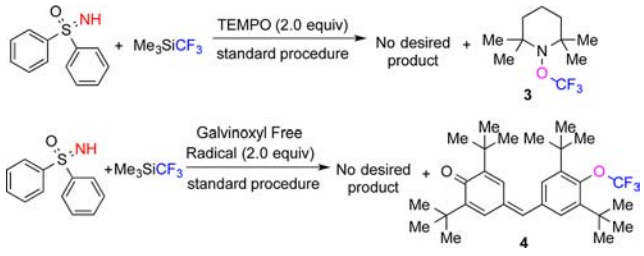


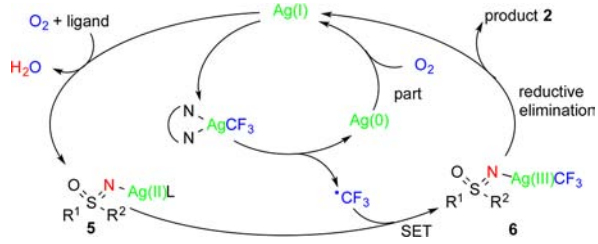
Table 2. Detection of the Trifluoromethyl Radical Adduct to TEMPO 3[a]

entry	sulfoximine	Me_3SiCF_3	Ag_2CO_3	1,10-phen	results
1	×	√	√	√	+
2	√	×	√	√	−
3	√	√	×	√	−
4	√	√	√	×	−
5	√	√	√	√	+

[a]Performed under standard conditions. For details, see the Supporting Information. "+" means positive result; adduct **3** was formed. "−" means negative result; adduct **3** remained undetected.

Based on these results, we suggest a mechanistic scenario as outlined in Scheme 3.[16] In the presence of the sulfoximine and

Scheme 3. Proposed Mechanism



the ligand, the silver(I) cation is oxidized by dioxygen to a silver(II) species (**5**).[17] An in situ formed chelate-stabilized $AgCF_3$ complex produces the detected trifluoromethyl radical and a Ag(0) species, which is oxidized to Ag(I) reentering the catalytic cycle.[18] The CF_3 radical reacts with **5** to give Ag(III) intermediate **6**.[19] Reductive elimination of **6**[20] provides product **2** and regenerates the silver(I) cation closing the catalytic cycle.

In conclusion, we have developed a new *N*-trifluoromethylation method providing unprecedented sulfoximine derivatives with good functional group tolerance. Important features of the process are (1) the establishment of a radical process and (2) the use of catalytic quantities of silver carbonate as inexpensive promotor functioning under base-free conditions. Synthetic extensions of this strategy are currently under investigation in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures along with copies of spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01537.

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Notes

The authors declare no competing financial interest.

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