C–H Activation

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Direct Trifluoromethylthiolation of Unactivated C(sp^3)–H Using Silver(I) Trifluoromethanethiolate and Potassium Persulfate**

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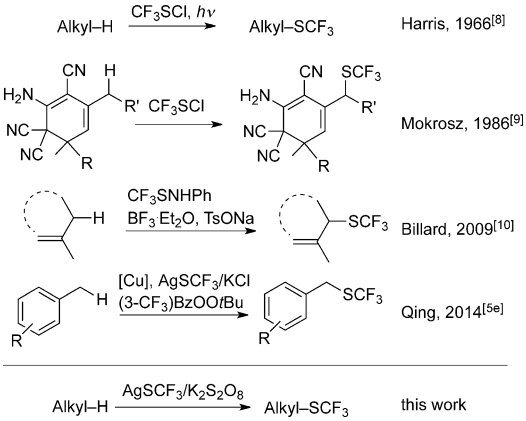
Abstract: *A practical and efficient method for the direct trifluoromethylthiolation of unactivated C(sp^3)–H bonds by $AgSCF_3/K_2S_2O_8$ under mild conditions is described. The reaction has a good functional-group tolerance and good selectivity. Initial mechanistic investigations indicate that the reaction may involve a radical process in which $K_2S_2O_8$ plays key roles in both the activation of the C(sp^3)–H bond and the oxidation of $AgSCF_3$.*

A trifluoromethylthio group (CF_3S) can significantly influence the chemical, physical, and biological properties of a parent substrate because of its strong electronegativity and high lipophilicity.[1] Considerable efforts have thus been devoted to the development of methods to introduce this group into organic molecules. Two major strategies for the chemical introduction of trifluoromethylthio groups were developed: the direct formation of C–S bonds (R–SCF_3) and the trifluoromethylation of thiols and their derivatives (RS–CF_3).[2] In recent years, several elegant methods have been reported for the electrophilic,[3] nucleophilic,[4] and oxidative direct trifluoromethylthiolation.[5] These methods enable the fast and efficient synthesis of various CF_3S-containing compounds.

In comparison to the recent progress made in the formation of C(sp^2)–SCF_3 or C(sp)–SCF_3 bonds, only few methods have been developed for the formation of C(sp^3)–SCF_3 bonds. Besides the classical halogen–fluorine exchange of polyhalogenomethyl thioethers or the trifluoromethylation of sulfur-containing compounds,[2] alkyltrifluoromethyl thioethers are mainly accessed by employing electrophilic[3a,l,6] or nucleophilic[7] trifluoromethylthiolation reagents. Although these methods efficiently lead to the desired alkyltrifluoromethylthioethers, they generally require prefunctionalized starting materials. From a preparative and atom-economical point of view, the direct trifluoromethylthiolation of an unactivated C(sp^3)–H bond constitutes the most straightforward approach to alkyltrifluoromethylthioethers. However, only few synthetic methods have been reported thus far (Scheme 1). Harris first reported in 1966 the free-radical



Scheme 1. Previous reports on the direct trifluoromethylthiolation of unactivated C(sp^3)–H bonds.

chain reaction of alkanes with the highly toxic gas trifluoromethanesulfenyl chloride (CF_3SCl).[8] Although various trifluoromethylthiolated isomers were successfully obtained, the reaction showed a narrow substrate scope and poor selectivity. In 1986, Mokrosz reported the direct trifluoromethylthiolation of the allylic H atom in alkylidenemalononitrile dimers by reaction with CF_3SCl.[9] In 2009, Billard and co-workers reported a method for the direct trifluromethylthiolation of allylic H atoms of hindered olefins with the electrophilic reagent $CF_3SNMePh$.[10] Very recently, Qing and co-workers disclosed the Cu-mediated direct trifluoromethylthiolation of a benzylic C–H bond.[5e] Thus, the development of reagent systems that can efficiently trifluoromethylthiolate the unactivated C(sp^3)–H bond under mild conditions is highly desirable.

On the other hand, unactivated C(sp^3)–H bonds, especially those that are not adjacent to an sp^2-hybridized C atom or a functional group that favors the formation of radicals or anions, exhibit the least reactivity, as they are less acidic and have no empty low-energy or filled high-energy orbitals that easily interact with orbitals of a metal center. Their selective functionalization under mild conditions represents a significant challenge and goal in modern synthetic chemistry.[11] Recently, the direct fluorination of unactivated C(sp^3)–H

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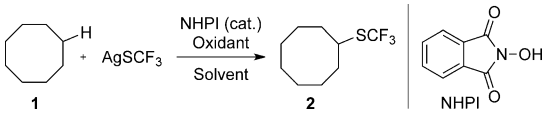
bonds has received great interest and impressive progress has been made.[12] Various C(sp^3)–F bond-containing compounds were efficiently and readily produced, typically through a radical pathway involving the generation and trapping of alkyl radicals with fluorine-transfer reagents. These important advances inspired us to investigate the formation of C(sp^3)–SCF_3 bonds through radical C(sp^3)–H activation and functionalization.

In order to test our hypothesis, we chose cyclooctane **1** as the model substrate for the direct trifluoromethylthiolation of C(sp^3)–H bonds. As radical initiator we used *N*-hydroxyphthalimide (NHPI), a precursor of the phthalimido-*N*-oxyl (PINO) radical and a well-known organocatalyst for the effective C(sp^3)–H activation by hydrogen abstraction.[13] For a CF_3S-transfer reagent system, we used $AgSCF_3$[14] as the convenient CF_3S resource and $K_2S_2O_8$ as the oxidant.[5g] When a mixture of **1** (1 equiv), NHPI (0.1 equiv), $AgSCF_3$ (1.5 equiv), and $K_2S_2O_8$ (2 equiv) in CH_3CN was stirred at 60 °C under Ar atmosphere for 12 h, the desired mono-trifluoromethylthiolated product **2** was formed in 43 % yield along with some poly-trifluoromethylthiolated products, which were identified by their characteristic signals in ^{19}F NMR spectroscopy and GC-MS mass spectrometry. Encouraged by this preliminary result, we optimized the reaction conditions (Table 1). When $AgSCF_3$ was used as the limiting reagent with 10 equiv of **1** under similar conditions, the desired mono-trifluoromethylthiolated product **2** was obtained in 82 % yield without the formation of any poly-trifluoromethylthiolated products (Table 1, entry 1). Later, we found that only a little excess of substrate (2 equiv) was required for the selective formation of the mono-trifluoromethylthiolated product, thus demonstrating the high efficiency of the reaction (Table 1, entry 2). The oxidant $K_2S_2O_8$ played an important role in the reaction, as no desired product was obtained in its absence or in the presence of other oxidants, such as $NaIO_4$, $PhI(OAc)_2$, $Pb(OAc)_4$ (Table 1, entries 3–5). A survey of the oxidant-to-substrate ratio showed that 2 equiv of $K_2S_2O_8$ gave the best yield (Table 1, entries 6 and 7). Among several common solvents that we screened, CH_3CN stood out as the best one and water was harmful for the reaction (Table 1, entries 8–13). A reaction temperature higher than 50 °C was required for an effective transformation, as no obvious conversion of $AgSCF_3$ was observed at lower temperatures (Table 1, entries 14–18). Interestingly, when the reaction was conducted at 50 °C, a longer reaction time (12 h) was required, as no reaction occurred within 4 h (Table 1, entry 16). Finally, the presence of the free silver cation was crucial for the reaction, because both the replacement of $AgSCF_3$ with $CuSCF_3$ and the addition of KCl (KCl/$AgSCF_3$ = 1:1) to the reaction mixture prevented the formation of the desired trifluoromethylthiolated product (Table 1, entries 19 and 20). To our surprise, the reaction proceeded smoothly in the absence of NHPI, which we originally considered as the key alkyl radical initiator (Table 1, entry 21). Based on these test reactions, the combination of $AgSCF_3$, $K_2S_2O_8$, and CH_3CN at 60 °C was established as the optimal conditions for the simple, mild, and efficient direct trifluoromethylthiolation of unactivated C(sp^3)–H bonds.

Table 1: Optimization of reaction conditions for trifluoromethylthiolation of cyclooctane.[a]

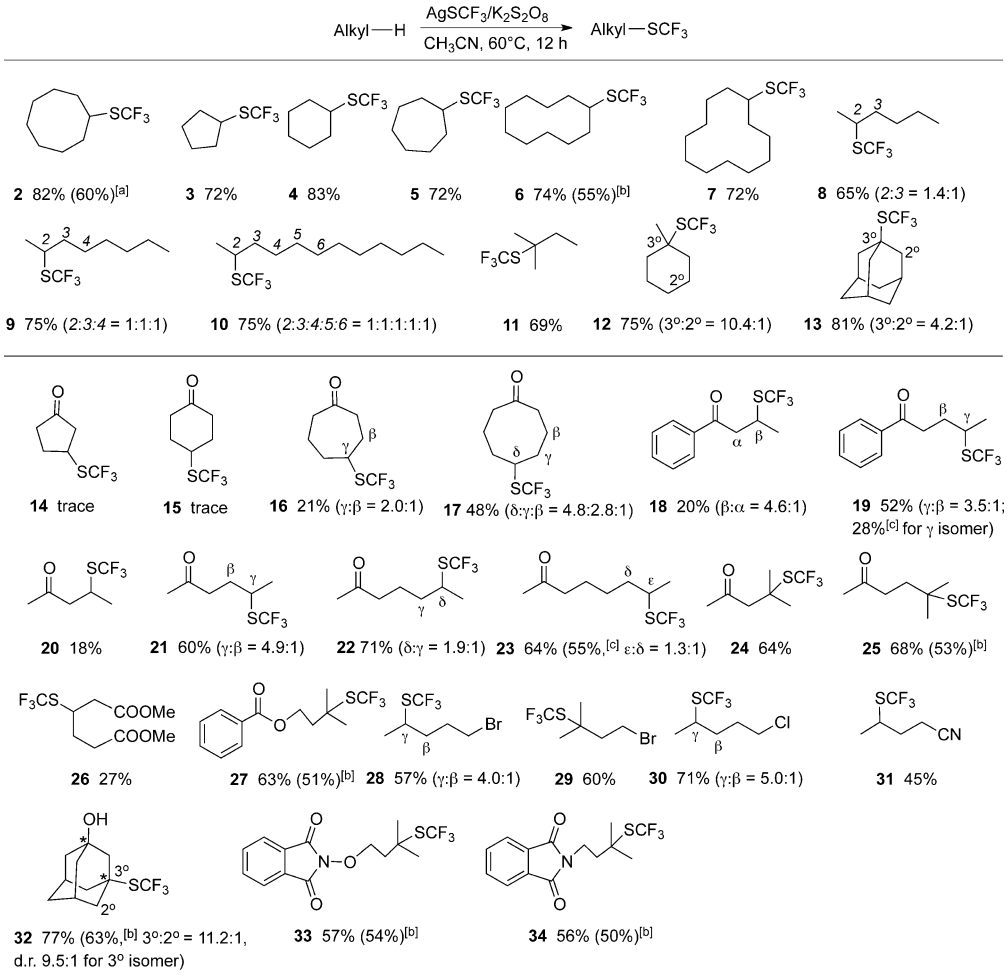


1 2 NHPI

Entry	Oxidant	Solvent	*T* [°C]	Yield [%][b]
1[c]	$K_2S_2O_8$	CH_3CN	60	82
2	$K_2S_2O_8$	CH_3CN	60	82
3	$NaIO_4$	CH_3CN	60	0
4	$PhI(OAc)_2$	CH_3CN	60	< 5
5	$Pb(OAc)_4$	CH_3CN	60	0
6	$K_2S_2O_8$[d]	CH_3CN	60	74
7	$K_2S_2O_8$[e]	CH_3CN	60	48
8	$K_2S_2O_8$	DMF	60	trace
9	$K_2S_2O_8$	DMSO	60	8
10	$K_2S_2O_8$	acetone	60	10
11	$K_2S_2O_8$	$ClCH_2CH_2Cl$	60	0
12	$K_2S_2O_8$	MeOH	60	0
13	$K_2S_2O_8$	CH_3CN/H_2O[f]	60	< 5
14	$K_2S_2O_8$	CH_3CN	40	0
15	$K_2S_2O_8$	CH_3CN	50	80
16[g]	$K_2S_2O_8$	CH_3CN	50	0
17	$K_2S_2O_8$	CH_3CN	70	81
18	$K_2S_2O_8$	CH_3CN	80	79
19[h]	$K_2S_2O_8$	CH_3CN	60	0
20[i]	$K_2S_2O_8$	CH_3CN	60	0
21[j]	**$K_2S_2O_8$**	**CH_3CN**	**60**	**82**

[a] Reaction conditions: cyclooctane (2.0 equiv), $AgSCF_3$ (0.2 mmol, 1.0 equiv), oxidant (2.0 equiv) and NHPI (0.1 equiv) in solvent (2 mL) under Ar atmosphere for 12 h. [b] Yields were determined by ^{19}F NMR spectroscopy with trifluorotoluene as an internal standard. [c] Cyclooctane (10 equiv) was used. [d] $K_2S_2O_8$ (3.0 equiv) was used. [e] $K_2S_2O_8$ (1.0 equiv) was used. [f] The reaction was conducted in CH_3CN/H_2O (1:0.1 v/v). [g] Reaction time: 4 h. [h] $CuSCF_3$ (1.0 equiv) was used instead of $AgSCF_3$. [i] KCl (1.0 equiv) was added to the reaction. [j] No NHPI was used. The entry in bold marks optimized reaction conditions.

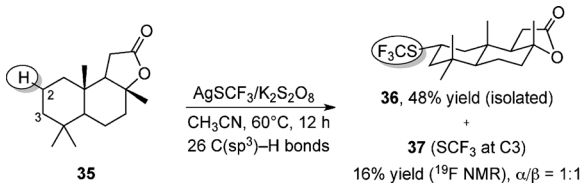
Various unactivated saturated hydrocarbons were then subjected to the optimized reaction conditions. All examined substrates were effectively transformed to the desired products in good yields (Scheme 2, **2**–**13**). The reaction also showed good site selectivity with preference for tertiary C–H bonds over secondary ones (**11**–**13**). The substrate scope of the reaction was investigated next. A variety of functional groups, such as ketones, esters, bromides, chlorides, alcohols, cyanates, and phthalimides, were well tolerated under the reaction conditions (**14**–**34**). Similarly, the direct C(sp^3)–H trifluoromethylthiolation occurred predominantly at tertiary C–H bonds. Cyclopentanone and cyclohexanone were not suitable substrates for the reaction, as only trace amounts of the desired products were observed, however, the reaction of cycloheptanone and cyclooctanone successfully resulted in the desired products (**14**–**17**). Various acyclic ketones underwent the trifluoromethylthiolation to give the desired products in acceptable yields (**18**–**25**). Notably, although the α position of the carbonyl group is generally the most reactive site in ketones, α-CF_3S products were not the major products and were commonly formed in negligible yields, which might be ascribed to the strong polar effect exerted by the carbonyl group in the C(sp^3)–H bond cleavage step in this reac-



Scheme 2. Scope of the direct trifluoromethylthiolation of various unactivated C(sp^3)–H bonds. Reaction conditions: substrate (2.0 equiv), $AgSCF_3$ (0.2 mmol, 1.0 equiv), oxidant (2.0 equiv) in acetonitrile (2 mL) under Ar atmosphere for 12 h. Yields were determined by ^{19}F NMR spectroscopy with trifluorotoluene as internal standard. The ratio of isomers was determined by ^{19}F NMR spectroscopy or GC-MS. Yields of isolated products are given in parentheses. [a] 5.0 mmol scale. [b] 1.0 mmol scale. 2° = secondary carbon center, 3° = tertiary carbon center.

tion.[13b,15] It should be mentioned that primary and secondary aliphatic alcohols could not be transformed in the reaction and no desired trifluoromethylthiolated products were observed, which might be due to the thermodynamically weaker C–H bond adjacent to the OH group. Indeed, when 1-adamantanol was used as the substrate, the trifluoromethylthiolation reaction proceeded smoothly to produce the desired trifluoromethylthiolated product in good yield (**32**). However, the reaction was not compatible with alkene and alkyne groups and a complicated reaction mixture was formed.

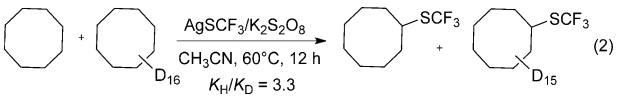
The possible scalability of the direct trifluoromethylthiolation of unactivated C(sp^3)–H bonds was demonstrated by the reaction of cyclooctane on a 5 mmol scale. The reaction proceeded smoothly and led to the isolated product in 60% yield (Scheme 2, **2**). Furthermore, to show the potential of the reaction in late-stage synthetic planning, (+)-sclareolide (**35**), a terpenoid natural product with antifungal and cytotoxic properties, was subjected to the direct C(sp^3)–H trifluoromethylthiolation [Eq. (1)]. Although **35** contains 26 aliphatic C(sp^3)–H bonds, the C2-equatorial trifluoromethylthiolated



35 (1)

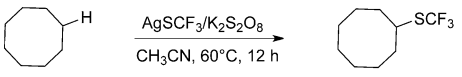
product **36** was isolated as the major product in 48% yield with minor amounts of product **37** (SCF_3 at C3). The structure of **36** was unambiguously determined by various analytical techniques, including X-ray single-crystal analysis (see the Supporting Information for details).

Some preliminary mechanistic studies on the direct trifluoromethylthiolation of C(sp^3)–H bonds were conducted in order to gain some insights into the reaction pathway. First, kinetic isotope effects (KIE) were measured by using cyclooctane and [D_{16}]cyclooctane (1:1) as the substrates under the standard reaction conditions [Eq. (2)], affording an intermolecular competitive KIE of 3.3. This large KIE suggested that



(2)

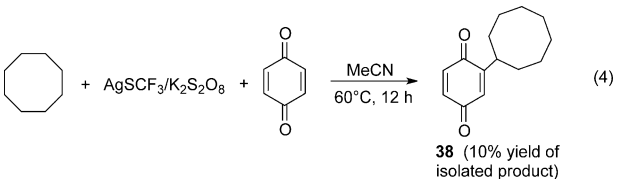
the cleavage of the C–H bond is the rate-limiting step. Second, an electron-transfer scavenger (1,4-dinitrobenzene), a radical inhibitor (hydroquinone), or a radical scavenger (2,2,6,6-tetramethyl-1-piperidinyloxy, TEMPO) were added to the reaction of cyclooctane [Eq. (3)]. The addition of 1,4-



(3)

no additive	82%
20 mol% dinitrobenzene	26%
20 mol% hydroquinone	52%
1.0 equiv TEMPO	66%

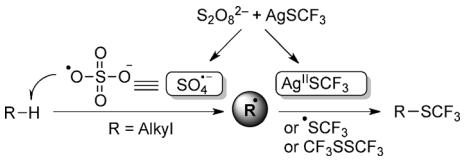
dinitrobenzene resulted in a sharp decrease in the yield, while the addition of hydroquinone and TEMPO did not have a significant impact on the reaction. These results might be due to the consumption of hydroquinone and TEMPO under the strongly oxidizing reaction conditions.[16] Moreover, the addition of benzoquinone to the reaction system resulted in the formation of product **38** [Eq. (4)].[7m] All these exper-



(4)

imental results indicate that the direct trifluoromethylthiolation of C(sp^3)–H bonds might proceed through a radical pathway. In addition, the reactivity of the C(sp^3)–H bonds increases in the order of primary < secondary < tertiary (see Scheme 2) and the main side product in most cases is CF_3SSCF_3 (^{19}F NMR signal at −46.65 ppm), thus demonstrating a radical reaction pathway as well.

Based on these preliminary results and previous reports on the C(sp^3)–H activation,[11–13] we propose a radical mechanism for the direct trifluoromethylthiolation of C(sp^3)–H bonds (Scheme 3). $K_2S_2O_8$ decomposes into a sulfate radical anion with the help of the silver cation present in the reaction system, which (as PINO) abstracts the hydrogen atom from a C(sp^3)–H bond in the substrate to generate the corresponding alkyl radical.[17] At the same time, the oxidation of



Scheme 3. Proposed mechanism for the direct trifluoromethylthiolation of unactivated C(sp^3)–H bond.

$AgSCF_3$ by $K_2S_2O_8$ affords the $Ag^{II}SCF_3$ species,[18] a CF_3S radical, or CF_3SSCF_3. The produced alkyl radical abstracts the CF_3S ligand of Ag(II)SCF_3 or couples with a CF_3S radical or CF_3SSCF_3 to afford the corresponding trifluoromethylthiolated product.

In conclusion, a direct trifluoromethylthiolation of unactivated C(sp^3)–H bond proceeds with $AgSCF_3$ and $K_2S_2O_8$. The reaction is mild, efficient, and practical and produced C(sp^3)–SCF_3 bonds with good functional-group tolerance and selectivity. Preliminary investigations show a radical reaction pathway with $K_2S_2O_8$ not only as an oxidant, but also as a good H atom abstractor. Further studies on the exploration of $K_2S_2O_8$ as an efficient radical initiator for other radical reactions are in progress.

Keywords: C–H activation · fluorine · radical reactions · synthetic methods · trifluoromethylthiolation

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