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Shelf-Stable Electrophilic Reagents for Trifluoromethylthiolation

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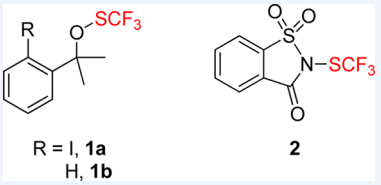
CONSPECTUS: Fluorine, which is the most electronegative element and has a small atomic radius, plays a key role in pharmaceutical, agrochemical, and materials sciences. One of the fluoroalkyl groups, the trifluoromethylthio group (CF_3S-), has been well-recognized as an important structural motif in the design of lead compounds for new drug discovery because of its high lipophilicity (Hansch lipophilicity parameter π = 1.44) and strong electron-withdrawing properties, which could improve the drug molecule's cell-membrane permeability and enhance its chemical and metabolic stability. While classic methods for the preparation of trifluoromethylthiolated compounds typically involve halogen−fluorine exchange reactions of polyhalogenomethyl thioethers or trifluoromethylation of sulfur-containing compounds under harsh reaction conditions, an alternative but more attractive strategy is direct trifluoromethylthiolation of the substrate at a late stage by employing an electrophilic trifluoromethylthiolating reagent. Although several electrophilic trifluoromethylthiolating reagents have been reported previously, these reagents either require a strong Lewis acid/Brønsted acid as an activator or suffer from a toxic nature or limited substrate scope. To address these problems, in late 2011 we initiated a project with the aim to develop new, shelf-stable, and highly reactive electrophilic trifluoromethylthiolating reagents that could easily install the trifluoromethylthio group at the desired positions of the drug molecule at a late stage of drug development. Inspired by the broad reactivity of the hypervalent iodine reagent, we initially discovered a highly reactive trifluoromethylthiolating reagent, trifluoromethanesulfenate **1a**. Structure−reactivity studies disclosed that the iodine atom of reagent **1a** does not play an important role in this reagent's reactivity. Consequently, a simplified second-generation electrophilic reagent, trifluoromethanesulfenate **1b**, was developed. In parallel, we developed another shelf-stable, highly reactive electrophilic reagent with a broad substrate scope, *N*-trifluoromethylthiosaccharin (**2**).



In this Account, we mainly describe our discovery of these two different types of electrophilic trifluoromethylthiolating reagents, trifluoromethanesulfenates **1a** and **1b** and *N*-trifluoromethylthiosaccharin **2**. Systematic studies showed that both types of reagents are highly reactive toward a wide range of nucleophiles, yet the substrate scopes of these two different types of reagents are complementary. In particular, reagents **1a** and **1b** are more reliable in transition-metal-catalyzed reactions such as copper-catalyzed trifluoromethylthiolation of aryl/vinyl/alkylboronic acids and silver-catalyzed decarboxylative trifluoromethylthiolation of aliphatic carboxylic acids as well as in the organocatalytic asymmetric trifluoromethylthiolation of β-keto esters and oxindoles. Reagent **2** is more electrophilic than reagents **1a** and **1b** and is more efficient for direct trifluoromethylthiolation with nucleophiles such as alcohols, amines, thiols, and electron-rich arenes. The ease in preparation, broad scope, and mild reaction conditions make reagents **1a**, **1b**, and **2** very attractive as general reagents that allow rapid installation of the trifluoromethylthio group into small molecules.

1. INTRODUCTION

With an extremely high Hansch lipophilicity parameter (π = 1.44),[1] the trifluoromethylthio group (CF_3S-) is generally considered as one of the privileged structural motifs in drug design since incorporation of the trifluoromethylthio group into a drug molecule generally makes it easier for the molecule to cross the cell membrane, thus improving the drug's pharmacokinetics and efficacy.[2] Not surprisingly, the number of trifluoromethylthiolated drugs and agrochemicals on the market, as well as trifluoromethylthiolated lead compounds at different development stages, is increasing quickly.[3] As a result, this high demand in medicinal chemistry has stimulated many research groups to develop efficient methods for the incorporation of this group into small molecules.[4,5] Earlier methods for trifluoromethylthiolation can be generalized as indirect strategies, typically involving halogen−fluorine exchange reactions of polyhalogenomethyl thioethers or trifluoromethylation of sulfur-containing compounds such as disulfides and thiols. Both of these methods require preformation of the thiolated precursors and suffer from either harsh conditions and/or limited substrate scope.[6] A more attractive strategy for incorporation of the $-SCF_3$ group into small molecules is direct trifluoromethylthiolation of the substrate by formation of a $C-SCF_3$ bond. In this regard, several elegant transition-metal-catalyzed direct trifluoromethylthiolation methods have recently emerged. These methods typically are conducted under mild conditions and are compatible with a variety of functional groups.[7,8] Nevertheless, more efficient catalysts are needed to improve the turnover numbers and turnover frequencies of these systems before they become more practical. An alternative and straightforward method for direct trifluorome-

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thylthiolation is to use electrophilic trifluoromethylthiolating reagents such as CF_3SCl, $PhNHSCF_3$, and $PhN(Me)SCF_3$.[9] However, CF_3SCl is a toxic gas,[10] which restricts its further applications. $PhNHSCF_3$ and $PhN(Me)SCF_3$, initially developed by Billard and Langlois,[11] are effective for trifluoromethylthiolation of alkenes,[12] alkynes,[12] indoles,[13] and Grignard and lithium reagents,[14] but a strong Lewis acid or Brønsted acid is required to activate these reagents.

With this background in mind and in hope of making original contributions to this field, we asked ourselves in late 2011 whether a shelf-stable yet highly reactive electrophilic trifluoromethylthiolating reagent with broad substrate scope could be developed. The development of such a reagent would be particularly valuable for those nonspecialized laboratories since it would not require specific skills and use of protective clothing and/or equipment. In particular, a reagent that would allow medicinal chemists to install the trifluoromethylthio group at specific positions in a predictable way would streamline the discovery of new lead compounds.

As described in this Account, two types of electrophilic trifluoromethylthiolating reagents (**1a**/**1b** and **2**) have been developed in our laboratory in the past several years. These shelf-stable reagents can be easily synthesized and scaled up. The superior reactivity of these reagents was further demonstrated by trifluoromethylthiolation of various nucleophiles such as electron-rich arenes, aryl-, vinyl-, and alkylboronic acids, alkynes, aldehydes, ketones, β-keto esters, amines, alcohols, and thiols. These reagents now serve as general and ideal reagents for the rapid installation of trifluoromethylthio groups into small molecules.

2. TRIFLUOROMETHANESULFENATES: PREPARATION AND REACTIVITY

2.1. Synthesis of Trifluoromethanesulfenate 1a and Structure Revision

The initial idea to invent an electrophilic trifluoromethylthiolating reagent was inspired by our own work on trifluoromethylation. In late 2010, we discovered a copper-catalyzed trifluoromethylation reaction of aryl- and vinylboronic acids with Togni's trifluoromethylated hypervalent iodine reagent. The reaction conditions were mild (reactions were typically conducted at 35 °C), and many functional groups were compatible.[15] What we learned from this chemistry is that the hypervalent iodine skeleton is an excellent platform to transfer a trifluoromethyl group to other molecules. We asked ourselves whether a trifluoromethylthio group could be easily transferred to small molecules in a similar way as with the trifluoromethylating reagent if an analogous trifluoromethylthio-substituted hypervalent iodine derivative could be prepared. It turned out that the preparation of compound **1a′** was challenging since the sulfide can be easily oxidized to form the disulfide CF_3SSCF_3. After many tries, we discovered that compound **1a′** could be generated in 51% yield when the reaction in tetrahydrofuran (THF) was conducted at 50 °C for 1 h.[16] Reagent **1a′** was isolated as a colorless stable liquid with a boiling point of 151−153 °C as determined by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA).[17] Reagent **1a′** was characterized by ^1H, ^{13}C, and ^{19}F NMR spectroscopy as well as elemental analysis. On the basis of our experience with hypervalent iodine reagents and the reactivities of reagent **1a′**, the structure of reagent **1a′** was initially proposed to be a trifluoromethylthio-substituted hypervalent iodine reagent. Very recently, Buchwald and coworkers[18] revised the structure of the reagent to be a trifluoromethanesulfenate (**1a**) on the basis of a combination of spectroscopic techniques, derivatization experiments, and crystal sponge technology (Figure 1).

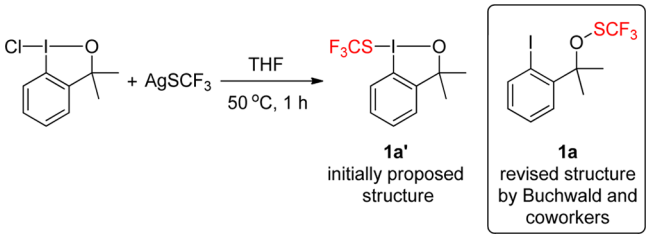
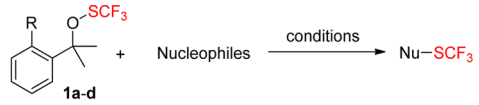


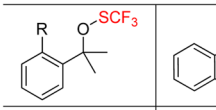
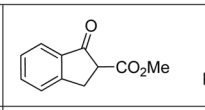
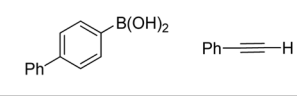
Figure 1. Preparation of the electrophilic trifluoromethylthiolating reagent, its initial proposed structure **1a′**, and the revised structure **1a**.

2.2. Structure−Reactivity Relationship Study and Synthesis of Trifluoromethanesulfenate 1b

One question that arose from the structure revision is the role of the iodine atom in the reactivity of the reagent **1a**. To probe whether the iodine substituent is critical for the reactivity of the trifluoromethylthiolating reagent, we synthesized a family of substituted trifluoromethanesulfenates and studied their structure−reactivity relationship. We found that substituted trifluoromethanesulfenates with or without the iodine atom showed similar reactivities toward several nucleophiles, including a β-keto ester, an arylboronic acid, and phenylacetylene (Table 1).[19] Subsequent studies showed that the simplified trifluoromethanesulfenate **1b**, which is shelf-stable and easily handled, can be used as a slightly less effective but much cheaper electrophilic trifluoromethylthiolating reagent compared with **1a**.

Table 1. Structure−Reactivity Relationship Studies of Trifluoromethanesulfenates



			
R = I, **1a**	98%	99%	99%
R = H, **1b**	95%	57%	98%
R = Br, **1c**	92%	57%	73%
R = Me, **1d**	99%	54%	90%

2.3. Reactions of Reagents 1a and 1b with Indoles

Indole is one of the privileged structural motifs in biologically active natural products such as amino acids and alkaloids. Development of efficient methods for trifluoromethylthiolation of indoles is of current interest. Direct electrophilic trifluoromethylthiolation of indoles represents a straightforward method for the preparation of trifluoromethylthiolated indoles.[13,20] The reactions of a variety of indoles with the electrophilic trifluoromethylthiolating reagents **1a** and **1b** in the presence of 10 mol % camphorsulfonic acid occurred smoothly after 48 h at 40 °C to give the corresponding trifluoromethylthiolated indoles in moderate to good yields, although

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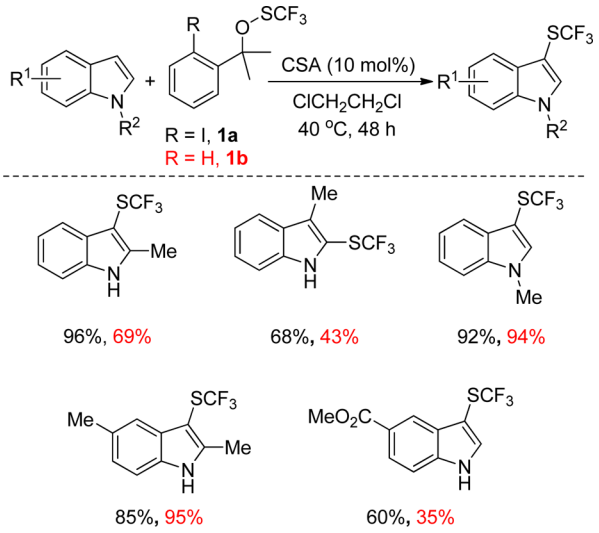
typically the reactions using reagent **1a** afforded higher yields than those using reagent **1b** (Chart 1).[17,19] Reactions of indoles

Chart 1. Brønsted Acid-Catalyzed Trifluoromethylthiolation of Indoles Using Reagents 1a and 1b

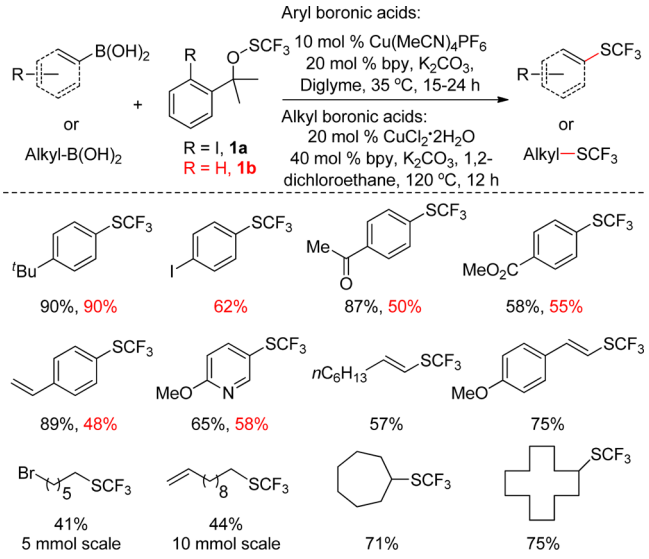


with electron-donating groups generally generated the trifluoromethylthiolated indoles in higher yields than those with electron-withdrawing groups. The reactions of 3-methylindole with reagents **1a** and **1b** formed the corresponding 2-trifluoromethylthiolated indole in 68% and 43% yield, respectively. Interestingly, when other electron-rich arenes were subjected to the same reaction conditions, low conversions were observed. A similar method for the preparation of trifluoromethylthiolated indoles using Billard's $PhNHSCF_3$ as the electrophilic trifluoromethylthiolating reagent required 2.5 equiv of *p*-toluenesulfonic acid to activate the reagent.[13] Likewise, the same reaction using Shibata's trifluoromethylthiolating reagent required the use of a copper catalyst.[20]

2.4. Reactions of Reagents 1a and 1b with Aryl-, Vinyl-, and Alkylboronic Acids

To overcome the limitation of the electrophilic aromatic trifluoromethylthiolation reaction, we turned our attention to direct trifluoromethylthiolation of organometallic nucleophiles such as Grignard reagents[14] and arylboronic acids.[8] Reactions of Grignard reagents with reagent **1b** are straightforward and give the trifluoromethylthiolated arenes in 70−85% yield after stirring in THF at 0 °C for 0.5 h.[19] However, Grignard reagents are generally not commercially available and are not compatible with a variety of functional groups. In this respect, easily available, stable, and crystalline arylboronic acids are ideal alternative nucleophiles. Indeed, reactions of various arylboronic acids with reagents **1a** and **1b** occurred in good to excellent yields when a combination of 10 mol % $Cu(CH_3CN)_4PF_6$ and 20 mol % bipyridine (bpy) was used as the catalyst (Chart 2).[16,19] Hetarylboronic acids were also trifluoromethylthiolated in good yields. Reactions using reagent **1b** as the electrophilic trifluoromethylthiolating reagent generally afforded slightly lower yields than those using reagent **1a**. Because a weak base (K_2CO_3) was used, functional groups such as bromo, iodo, aldehyde, enolizable ketone, ester, and alkene were tolerated, as shown by the selected examples in Chart 2. In addition, vinylboronic acids also reacted under the

Chart 2. Copper-Catalyzed Trifluoromethylthiolation of Aryl-, Vinyl-, and Alkylboronic Acids Using Reagents 1a and 1b



standard conditions to generate the trifluoromethylthiolated alkenes in good to excellent yields. Interestingly, shortly thereafter Rueping and we simultaneously discovered that the same reaction can be achieved by using trifluoromethylthiolated phthalimide as the trifluoromethylthio source.[8c,d]

Transition-metal-catalyzed cross-coupling of alkylboronic acids is usually more difficult than that of aryl- and vinylboronic acids, mainly because of their slower transmetalation to the transition-metal intermediates.[21] Consistent with this trend, reactions of alkylboronic acids with reagent **1a** required the reaction temperature to be increased to 120 °C.[22] At this temperature, reactions of primary and secondary alkylboronic acids occurred with full conversion after 12 h to give the trifluoromethyl thioethers in good to excellent yields (Chart 2).

2.5. Iron-Catalyzed Hydrotrifluoromethylthiolation of Alkenes with Reagent 1b

An alternative method for the synthesis of alkyl trifluoromethyl thioethers is radical trifluoromethylthiolation. Inspired by Boger's pioneering work,[23] we discovered that alkyl radicals can easily be generated by the iron-mediated reaction of BH_3 with alkenes in 1:1 CH_3CN/H_2O mixed solvent.[24] Subsequent trapping of the alkyl radicals with reagent **1b** forms the alkyl trifluoromethyl thioethers (Chart 3). Overall, the reaction constitutes a formal Markovnikov-selective hydrotrifluoromethylthiolation of alkenes. The reaction is particularly fast and typically leads to full conversion within 30 min at 0 °C. Radical cyclization and radical clock experiments suggested that the reaction proceeds through a free radical process.

2.6. Silver-Catalyzed Decarboxylative Trifluoromethylthiolation of Alkyl Carboxylic Acids with Reagent 1a in Aqueous Emulsion

Another approach for the generation of alkyl radicals is the Hunsdiecker reaction of alkyl carboxylic acids.[25] Classical Hunsdiecker reaction conditions, however, led to less than 12% yield of the desired product in the reaction of adamantane-1-carboxylic acid with reagent **1a**. We were pleased to find that the addition of 0.2 equiv of sodium dodecyl sulfate (SDS) dramatically accelerated the decarboxylative trifluoromethylthiolation reaction.[26] Not only secondary but also tertiary alkyl

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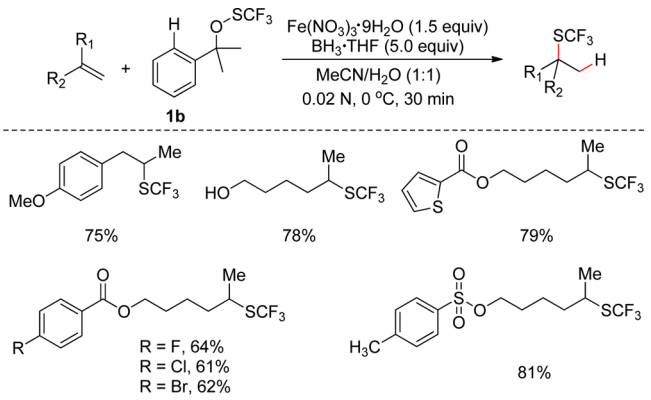
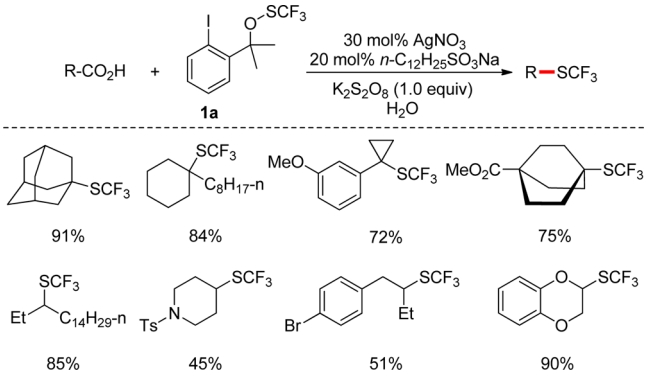
Chart 3. Iron-Catalyzed Trifluoromethylthiolation of Alkenes Using Reagent 1b



carboxylic acids underwent decarboxylative trifluoromethylthiolation to generate the alkyl trifluoromethyl thioethers in good to excellent yields (Chart 4).

Chart 4. Silver-Catalyzed Decarboxylative Trifluoromethylthiolation of Aliphatic Carboxylic Acids Using Reagent 1a

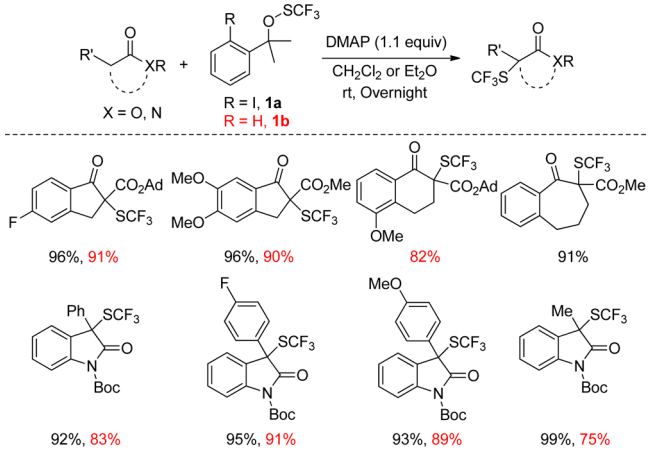


The formation of tertiary alkyl trifluoromethyl thioethers is particularly attractive since few other methods for the preparation of these compounds have been reported. Functional groups such as chloro, bromo, esters, and electron-rich arenes were compatible with the reaction conditions. The reactions were conducted in water, thus demonstrating another advantage of the reaction, since water is cheap, nontoxic, and nonflammable and also shows extraordinary solvent effects. It was observed that an emulsion was formed when SDS was added to the reaction mixture. Reagent **1a** was then emulsified in a solution of SDS and water to form "oil-in-water" droplets. The alkyl radical generated from the silver(II) carboxylate in an "oil-in-water" droplet via a concerted decarboxylation pathway then reacted with reagent **1a** to form the corresponding product.

2.7. Reactions of Reagents 1a and 1b with β-Keto Esters and Oxindoles

The reactions of hard nucleophiles such as arylboronic acids and alkyl carboxylic acids with reagents **1a** and **1b** generally required the presence of transition-metal catalysts. The reactions of soft nucleophiles such as β-keto esters[20] and oxindoles, however, occurred in the absence of any transitional-metal catalyst.[16,19] With 4-dimethylaminopyridine (DMAP) as the base, a variety of functionalized β-keto esters derived from indanone, tetralone, and 1-benzosuberone reacted with reagents **1a** and **1b** to give the corresponding products in high yields (Chart 5). Reactions of open-chain β-keto esters

Chart 5. Reactions of Reagents 1a and 1b with β-Keto Esters and Oxindoles



with active methylene moieties, however, were messy. It is likely that the product was more reactive than the starting material and that many other side reactions therefore took place.

Under similar reaction conditions, reactions of functionalized oxindoles bearing a substituent at the 3-position with reagents **1a** and **1b** also generated the trifluoromethylthiolated oxindoles in excellent yields (Chart 5).[19]

2.8. Asymmetric Trifluoromethylthiolations of β-Keto Esters and Oxindoles Using Reagents 1a and 1b

Since trifluoromethylthiolations of β-keto esters and oxindoles were mediated by DMAP, as a logical extension, an asymmetric trifluoromethylthiolation reaction could be realized when an optically pure nitrogen-based Lewis base was used. Not surprisingly, the reaction of the β-keto ester derived from indanone with reagent **1a** occurred with full conversion after 24 h at 40 °C to give the trifluoromethylthiolated β-keto ester with 92% ee when quinine, a natural alkaloid and a veteran organocatalyst, was used as the catalyst.[27] The hydroxyl group of quinine is important for the high reactivity and enantioselectivity of the reaction, as the reaction was shut down when the hydroxyl group was protected by an ester group. Reactions of a variety of adamantyl β-keto esters derived from indanones with reagent **1a** proceeded with excellent enantioselectivity. The enantioselectivity was not significantly affected by the nature or the position of the substituent of the β-keto ester derivative. Likewise, reactions of various *tert*-butoxycarbonyl (Boc)-protected 3-substituted oxindoles also occurred with high enantioselectivity under similar conditions.[28] Interestingly, the reactions of 3-aryloxindoles generated the corresponding trifluoromethylthiolated products with 73–87% ee, while the reactions of 3-alkyloxindoles formed the products with 95–99% ee, as shown by the selected examples in Chart 6. Thus, a highly enantioselective method for the construction of a SCF_3-substituted quaternary stereogenic center was established. Shortly thereafter, Gade and co-workers reported a copper-catalyzed asymmetric trifluoromethylthiolation of β-keto esters using reagent **1a** as the trifluoromethylthio source.[29a] In addition, two other methods for highly selective

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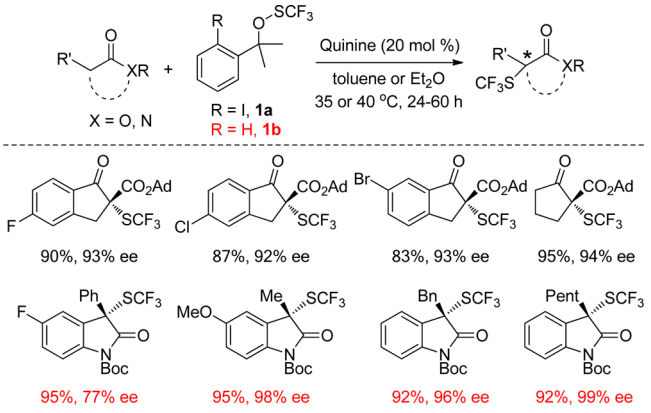
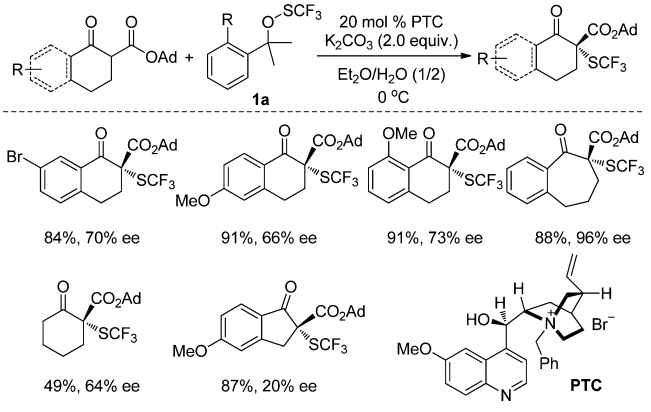
Chart 6. Asymmetric Trifluoromethylthiolations of β-Keto Esters and Oxindoles Using Reagents 1a and 1b



asymmetric trifluoromethylthiolation of β-keto esters and 3-aryloxindoles using *N*-trifluoromethylthiophthalimide or an in situ-generated electrophilic trifluoromethylthiolating reagent were reported by the groups of Rueping[29b,c] and Liu and Tan,[29d] respectively.

Out of our expectation, when an enolizable β-keto ester with a cyclic six- or seven-membered ring derived from tetralone or 1-benzosuberone was subjected to the standard conditions, less than 5% of the β-keto ester was converted to the corresponding trifluoromethylthiolated compound. We then sought to use a cinchona alkaloid-based chiral phase-transfer catalyst (PTC) to affect the reactivity and enantioselectivity of these substrates. When the PTC derived from quinine was used as the catalyst, combined with K_2CO_3 as the base and 1:2 Et_2O/H_2O mixed solvent, a general protocol for enantioselective trifluoromethylthiolation of six- or seven-membered-ring β-keto esters was developed (Chart 7).[27] Interestingly, under PTC conditions, β-keto esters derived from indanone reacted with low ee (<25% ee), in contrast to the high enantioselectivity obtained with quinine as the catalyst.

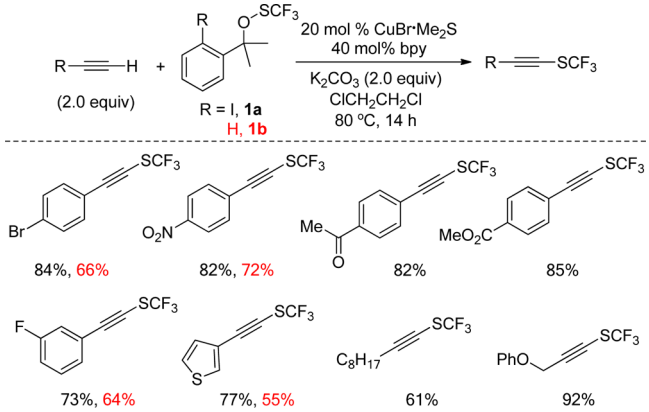
Chart 7. Asymmetric Trifluoromethylthiolation of β-Keto Esters under Phase-Transfer-Catalyst Conditions



2.9. Reaction of Reagents 1a and 1b with Alkynes

Having establishing efficient methods for the construction of $C(sp^2)-SCF_3$ and $C(sp^3)-SCF_3$ bonds, our next target was to develop an efficient method for the formation of $C(sp)-SCF_3$ bonds.[30] Copper was found to be an effective catalyst for this transformation.[16] The reactions of alkynes with reagents **1a** and **1b** occurred smoothly in 1,2-dichloroethane after 14 h at 80 °C to give the trifluoromethylthiolated alkynes in high yields when a combination of $CuBr{\cdot}SMe_2$ (20 mol %) and 2,2′-bipyridine (bpy) (40 mol %) was used as the catalyst. Aliphatic- and heteroaryl-substituted alkynes also reacted under standard conditions to give the corresponding alkynyl trifluoromethyl thioethers in satisfactory yields (Chart 8). Trifluoromethylthiolated alkynes may serve as important building blocks in cyclization reactions such as Diels–Alder reactions and 1,3-dipolar cycloadditions for the construction of many trifluoromethylthiolated arenes and heteroarenes.[39]

Chart 8. Trifluoromethylthiolation of Alkynes Using Reagents 1a and 1b



3. *N*-TRIFLUOROMETHYLTHIOSACCHRIN: PREPARATION AND REACTIVITY

In a parallel effort to develop a general electrophilic trifluoromethylthiolating reagent that mimics the reactivity of *N*-bromosuccinimide (NBS), we designed three trifluoromethylthiolated NBS analogues, *N*-trifluoromethylthiosuccinimide, *N*-trifluoromethylthiophthalimide, and *N*-trifluoromethylthiosaccharin, that may exhibit high reactivity toward a broad scope of nucleophiles. *N*-Trifluoromethylthiosuccinimide[31] and *N*-trifluoromethylthiophthalimide[32] were previously prepared from toxic and gaseous CF_3SCl, thus limiting their applications, while *N*-trifluoromethylthiosaccharin (**2**) had not been reported previously. We then developed a new and convenient method for the preparation of these reagents by reactions of NBS, *N*-bromophthalimide, and *N*-chlorosaccharin, respectively, with $AgSCF_3$ in acetonitrile at room temperature (eqs 1–3).[8d,33] Alternatively, **2** could be prepared in 86% yield via a two-step procedure involving initial treatment of saccharin with *tert*-butyl hypochlorite in methanol at room temperature for 5 min followed by further reaction with $AgSCF_3$ in CH_3CN for 10 min. The reaction can be easily scaled up to 20.0 g quantities, and reagent **2** was isolated as a white solid in 84% yield.

Interestingly, these reagents showed dramatically different reactivities. The reaction of 2-(naphthalen-2-yl)ethanol with **2** in the presence of 2.3 equiv of triethylamine formed the trifluoromethanesulfenate in quantitative yield after 5 min at room temperature.[33a] In contrast, less than 16% yield was detected when *N*-trifluoromethylthiosuccinimide or *N*-trifluoromethylthiophthalimide was used, and no improvements were observed with an elongated reaction time (12 h) or increased reaction temperature (80 °C) (Figure 2). This serendipitous

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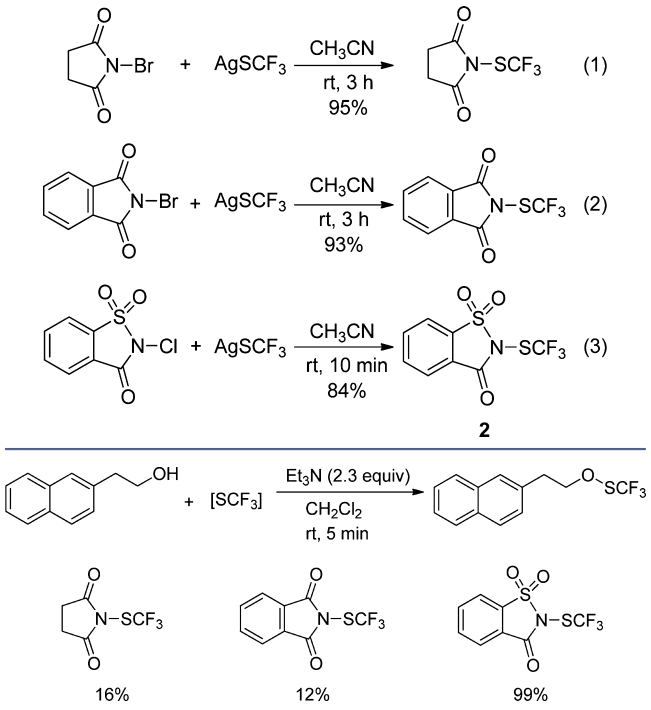


Figure 2. Different reactivities of the three trifluoromethylthiolating reagents.

discovery indicates that reagent **2** displays remarkably higher reactivity than the other two trifluoromethylthiolating reagents, thus encouraging us to study its reactivity toward various nucleophiles in detail.

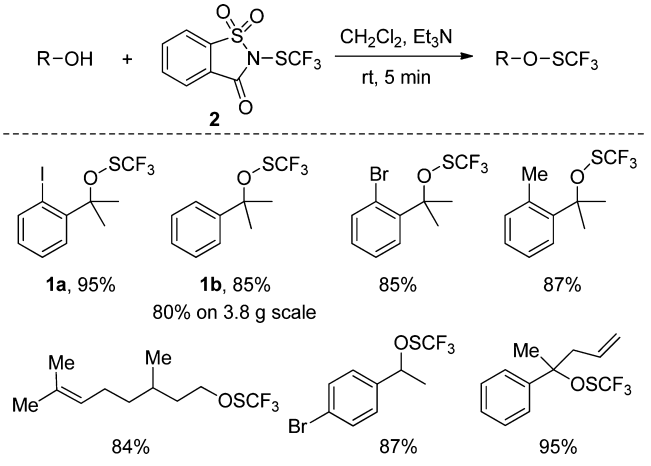
3.1. Reaction of Reagent 2 with Alcohols

As demonstrated above, trifluoromethanesulfenate **1a** is a highly reactive electrophilic trifluoromethylthiolating reagent. However, its preparation requires several steps, and the overall efficiency is not high enough for large-scale synthesis. The development of *N*-trifluoromethylthiosaccharin provided a solution to this problem. Mixing the corresponding alcohol and **2** in dichloromethane at room temperature for 5 min afforded reagent **1a** in 87% yield when 2.3 equiv of triethylamine was used as the base. Likewise, analogous tertiary alcohols could be converted into the corresponding trifluoromethanesulfenates in excellent yields.[33a] Notably, these reactions can be easily scaled up without a decrease in yield. For example, the reaction of 2-phenylpropan-2-ol (20 mmol) with reagent **2** generated trifluoromethanesulfenate **1b** in 80% yield on a 3.8 g scale. Other alcohols such as primary and secondary alcohols were also readily converted into trifluoromethanesulfenates in excellent yields (Chart 9).

3.2. Reaction of Reagent 2 with Amines

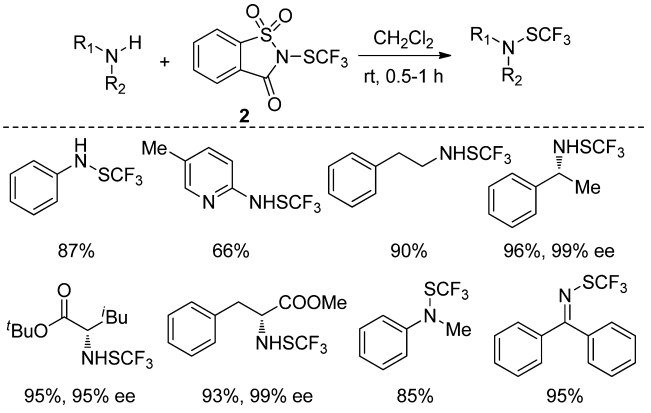
The trifluoromethylsulfanylamine moiety (CF_3SN), which has a high Hansch lipophilicity parameter (π = 1.50), could be of interest to medicinal chemists in the development of potential medicinally active compounds. However, few methods for the preparation of these compounds have been reported. Previously reported methods for the preparation of trifluoromethylsulfanylamines required either the use of diethylaminosulfur trifluoride (DAST)[11] or CF_3SCl[40] or the presence of 1.1 equiv of *n*BuLi as the base when Billard's reagent was used as the electrophilic trifluoromethylthiolating reagent.[34] Simple mixing with **2** in dichloromethane at room temperature for 1 h

Chart 9. Trifluoromethylthiolation of Alcohols Using Reagent 2



resulted in the trifluoromethylthiolation of a variety of primary or secondary alkyl amines and arylamines in excellent yields. Importantly, optically pure alkylamines, including α-amino esters, which are valuable for biochemists, were readily converted to the trifluoromethylthiolated amines in excellent yields without racemization (Chart 10).[33a]

Chart 10. Trifluoromethylthiolation of Amines Using Reagent 2



3.3. Reaction of Reagent 2 with Thiols

Another family of nucleophiles that reacted with *N*-trifluoromethylthiosaccharin was thiols. Few methods for the preparation of aryl trifluoromethyl disulfide were reported previously, and the known methods typically required the use of highly toxic CF_3SCl or CF_3SSCF_3.[34,35] The reactions of reagent **2** with a variety of aryl and heteroaryl thiols occurred within 1 h at room temperature to give the trifluoromethyl-substituted disulfides in excellent yields (Chart 11). Functional groups such as fluoro, chloro, bromo, and nitro were compatible with the reaction conditions. Alkyl thiols also reacted with reagent **2** to provide the disulfide products in good yields. Thus, a straightforward method for the preparation of trifluoromethyl-substituted disulfides, a family of potentially useful intermediates, was developed.[33a]

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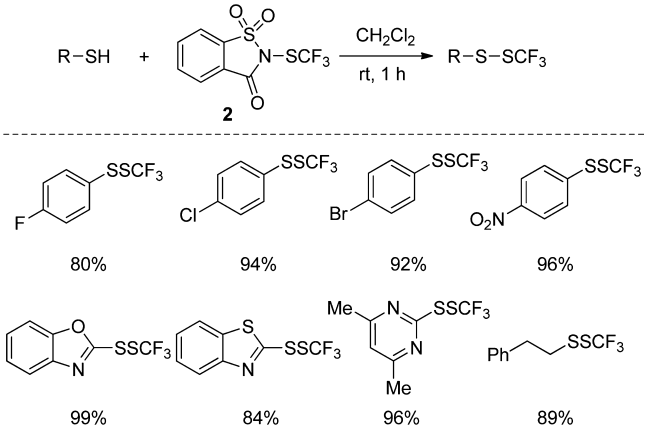
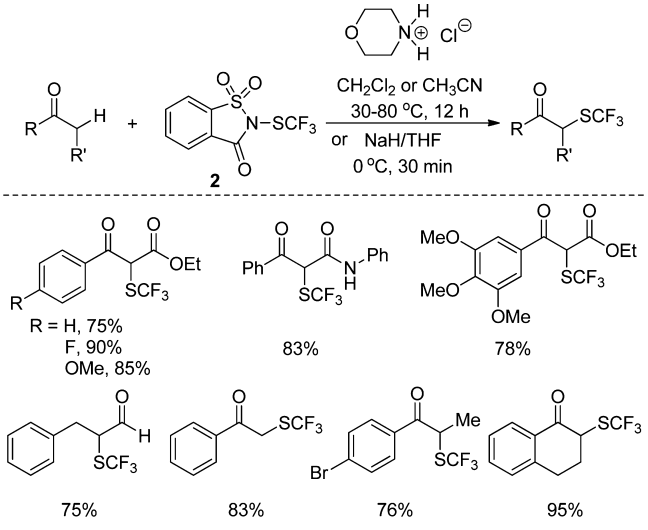
Chart 11. Trifluoromethylthiolation of Thiols Using Reagent 2



3.4. Monotrifluoromethylthiolation of Carbonyl Nucleophiles Using Reagent 2

α-Monotrifluoromethylthiolated carbonyl compounds are of current interest because the carbonyl moiety is an important structural motif in many bioactive natural products and drug molecules. Selective α-monotrifluoromethylthiolation of carbonyl compounds represented an unsolved problem until very recently, when several methods emerged to address this challenge.[20,36] We found that when NaH was used as the base, reactions of acyclic β-keto esters with reagent **2** occurred to afford the monotrifluoromethylthiolated β-keto esters in excellent yields after 0.5 h at 0 °C.[33a] Similarly, acyclic β-keto amides could also be monotrifluoromethylthiolated in good yields. Reactions of aldehydes and ketones were much less effective when they were conducted using NaH as the base. Instead, morpholine hydrochloride was a more effective catalyst for α-monotrifluoromethylthiolation of aldehydes and ketones. In the presence of 30 mol % morpholine hydrochloride, the reactions of several aldehydes and ketones with reagent **2** occurred smoothly to give the monotrifluoromethylthiolated products in good yields (Chart 12).[16,33a]

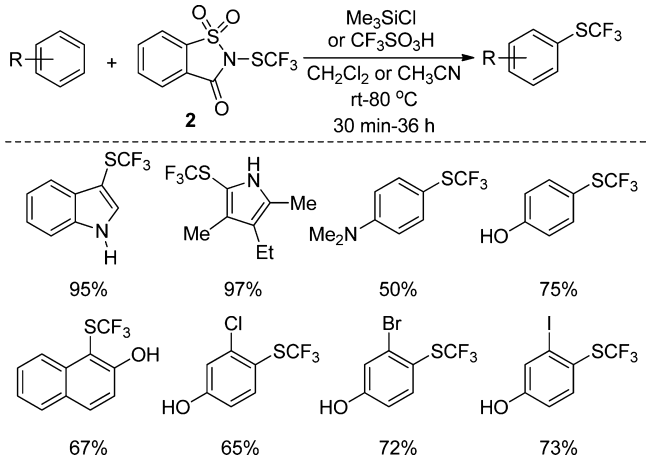
Chart 12. Monotrifluoromethylthiolation of Carbonyl Nucleophiles Using Reagent 2



3.5. Electrophilic Aromatic Trifluoromethylthiolation of Electron-Rich Arenes Using Reagent 2

Conceptually, electrophilic aromatic trifluoromethylthiolation of electron-rich arenes is of fundamental interest because it represents a straightforward method for the preparation of trifluoromethylthiolated arenes. However, very few electrophilic trifluoromethylthiolating reagents except toxic CF_3SCl undergo electrophilic aromatic substitution (S_EAr) reactions, as mentioned in section 2.3.[6,13,37,38] Strikingly, *N*-trifluoromethylthiosaccharin was highly reactive in S_EAr reactions when Me_3SiCl or triflic acid was used as activator.[33a] A variety of electron-rich arenes reacted with reagent **2** to give the corresponding trifluoromethylthiolated arenes in high yields (Chart 13). For example, reactions of phenol and *N*,*N*-dimethylaniline gave exclusively the para-trifluoromethylthiolated products in good yields. Similarly, electrophilic trifluoromethylthiolation of 2-naphthanol produced 1-trifluoromethylthio-2-naphthanol in 67% yield. Notably, 3-chloro, 3-bromo-, and 3-iodophenol were also site-selectively converted into trifluoromethylthio-substituted arenes in acceptable yields. The ability to selectively incorporate the trifluoromethylthio group into arenes in a predictable manner demonstrates the superior reactivity of **2**.

Chart 13. Friedel–Crafts-Type Trifluoromethylthiolation of Electron-Rich Arenes Using Reagent 2



4. COMPARISON OF THE REACTIVITIES OF TRIFLUOROMETHANESULFENATES 1A AND 1B AND *N*-TRIFLUOROMETHYLTHIOSACCHARIN 2

Reagents **1a**/**1b** and **2** constitute two different families of highly reactive electrophilic trifluoromethylthiolating reagents that allow for the efficient introduction of the trifluoromethylthio group into a wide range of substrates. Nevertheless, the substrate scopes of these two types of reagents are complementary. Reagents **1a** and **1b** show better reactivity than reagent **2** in transition-metal-catalyzed reactions such as copper-catalyzed trifluoromethylthiolation of aryl/vinyl/alkylboronic acids and silver-catalyzed decarboxylative trifluoromethylthiolation of aliphatic carboxylic acids. On the other hand, reagent **2** is more electrophilic than reagents **1a** and **1b** and therefore is more suitable for direct trifluoromethylthiolation of nucleophiles such as amines, alcohols, thiols, and electron-rich arenes. For example, the copper-catalyzed reaction of 2-phenylethylboronic acid with reagent **1a** afforded the product

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in 74% yield after 12 h at 120 °C, while the same reaction using reagent **2** as the electrophilic trifluoromethylthiolating reagent gave only a trace amount of the coupled product. On the other hand, reagent **2** displays much higher reactivity than reagent **1a** and **1b** in direct trifluoromethylthiolating reactions of nucleophiles such as alcohols, amines, and thiols. For example, reagents **1a** and **1b** themselves were prepared from reagent **2**. Similarly, electrophilic aromatic substitution of electron-rich arenes such as indoles, pyrroles, phenols, and anilines with reagent **2** formed the trifluoromethylthiolated products in good yields, while reagent **1a** reacted only with indoles and gave much lower yields when other electron-rich arenes were employed.

5. CONCLUSION

During the past several years, we have successfully developed two families of electrophilic trifluoromethylthiolating reagents: trifluoromethanesulfenates **1a** and **1b** and *N*-trifluoromethylthiosaccharin **2**. Both types of reagents are highly reactive toward a wide range of nucleophiles, yet the substrate scopes of these reagents are complementary. In particular, reagents **1a** and **1b** are more reliable in transition-metal-catalyzed reactions such as copper-catalyzed trifluoromethylthiolation of aryl/vinyl/alkylboronic acids and silver-catalyzed decarboxylative trifluoromethylthiolation of aliphatic carboxylic acids as well as in organocatalytic asymmetric trifluoromethylthiolation of β-keto esters. Reagent **2** is more electrophilic than reagents **1a** and **1b** and thus is more efficient for direct electrophilic trifluoromethylthiolation. During the same time periods, several other electrophilic trifluoromethylthiolating reagents, such as trifluoromethanesulfanylamides developed by Billard and Langlois, the trifluoromethanesulfonyl hypervalent iodonium ylide developed by Shibata, and *N*-trifluoromethylthiophthalimide, which was initially discovered by Munavali but its synthesis was recently improved by us and Rueping, have also been introduced.[8c,d,11,20,37a] Although no reagent is optimal for all substrates, we believe that by judicious choices from among the available electrophilic trifluoromethylthiolating reagents, efficient syntheses of trifluoromethylthiolated molecules can now be achieved on both small and large scales.

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Notes

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