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Letter

S-(Methyl-d_3) Arylsulfonothioates: A Family of Robust, Shelf-Stable, and Easily Scalable Reagents for Direct Trideuteromethylthiolation

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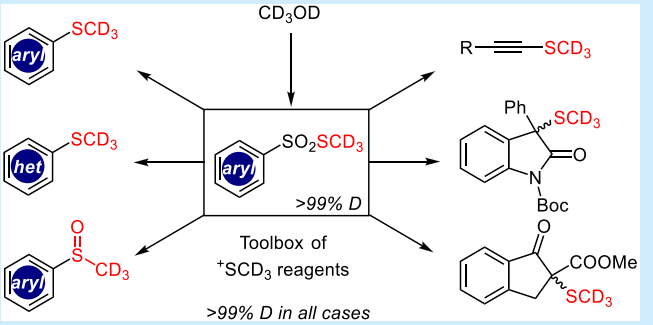
ABSTRACT: A family of electrophilic deuterated methylthiolating reagents, *S*-(methyl-d_3) arylsulfonothioates, was developed in two or three steps from cheap d_4-MeOH in high yields. *S*-(Methyl-d_3) arylsulfonothioates represent a kind of powerful deuterated methylthiolating reagent and allow modular trideuteromethylthiolation with a variety of nucleophiles or electrophiles including aryl(hetero) iodides, boronic acids esters, terminal alkynes, diazonium salts, β-ketoester, and oxindole under mild reaction conditions. A structure−reactivity research (SAR) study was conducted and provided a new avenue for the development of deuterated methylthiolating reagents and efficient methodology for trideuteromethylthiolation.



Deuterium-labeled organic compounds play a prevalent role in many critical areas of pharmaceuticals, materials, and organic chemistry research.[1] Owing to the so-called kinetic isotope effect (KIE), the deuterium atom differs greatly from the common hydrogen atom in both physical, chemical, and biological properties, resulting in its broad applications in NMR spectroscopy studies, mechanistic investigations of organic reactions, and other critical research areas (Figure 1a, left).[2] For example, austedo, a modified tetrabenazine for the treatment of Huntington's disease, has been approved as the first deuterated drug by FDA in 2017 (Figure 1a, left).[3]

Methylation of the specific molecules has already been recognized as an important and critical method for the structural modification of biological molecules because of the well-known "magic methyl effect".[4] Among the numerous derivatives of the methyl group, substituted methyl sulfides, sulfoxides, and related sulfones are found to be core structural scaffolds in pharmaceutical industry as examples of good partners of sulfur and methyl groups (Figure 1a, middle).[5] Moreover, enhanced biological ability and reduced toxicity of metabolites were achieved when the hydrogen atom on the methyl group was replaced by a deuterium atom.[6] From the viewpoint of synthetic and medicinal chemistry, deuterium labeling of currently existing drugs and/or study of drug candidates containing methyl sulfides is very promising and will be beneficial to drug discovery, expanding the diversity and complexity of the deuterium-labeled research.[6]

The traditional strategy for the construction of trideuteromethyl sulfides is the trideuteromethylation of corresponding thiols, and elegant processes have been disclosed by utilizing newly designed electrophilic CD_3 reagents (Figure 1b).[7] Compared to the above strategies (indirect method) requiring toxic and specific starting materials such as thiols, direct trideuteromethylthiolation will provide an attractive route for the introduction of the SCD_3 moiety directly, widely broadening the scope of the suitable substrates. Along this line of thought, easily accessible yet shelf-stable trideuteromethylthiolating reagents are essential for achieving this nice transformation (Scheme 1b). Furthermore, the degree of deuteration (>99%) is also one of most crucial factors for the evaluation on the efficiency of the trideuteromethylthiolation, while previous reports on the deuterated level mostly depend on the purity of the starting materials. For example, Wang described a novel synthetic route to prepare $PhSO_2SCD_3$ with 97% D incorporation in unknown yield from TDMSOI (97% D) in 2020.[8] *S*-Methyl-d_3 benzenesulfonothioate is a colorless liquid, and its synthetic utilities are only limited to the radical reaction on the trideuteromethylthiolation of diazonium salts, and other important applications such as the enantioselective process remain explored. Chen developed *S*-(methyl-d_3) 4-methylbenzenesulfonothioate from "*in situ*" generated CD_3OTf as the trideuteromethylating source, allowing for direct trideuteromethylthiolation of various nucleophiles such as boronic acids.[9]

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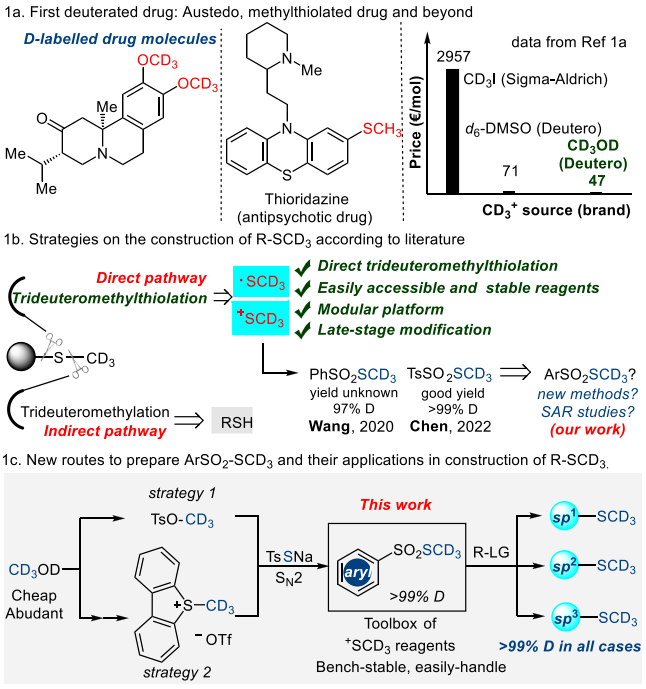
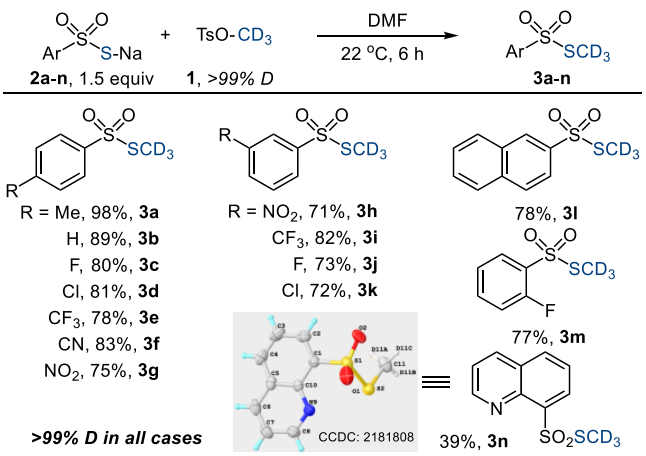


Figure 1. Selective strategies and thiolating reagents for C−S bond formation and our proposal.

Scheme 1. Scope of the *S*-(Methyl-d_3) Arylsulfonothioates[a]



[a]Substrate scope of $ArSO_2SNa$ (3.0 mmol scale) with $TsOCD_3$. For detailed reaction conditions, see the Supporting Information.

Nevertheless, structure−reactivity relationship (SAR) studies of a reagent provide the impetus for the modification of reactivity and stability of the compound by replacing different functional groups on the specific sites of the molecules. Design and synthesis of a family of novel electrophilic deuterated methylthiolating reagents with high efficiency and low cost will definitely provide a comprehensive understanding and synthetic options for organic and medicinal chemists, especially on the late-stage modifications of bioactive compounds.[10] Herein, we describe two new, economic, and practical approaches to access a toolbox of *S*-(methyl-d_3) arylsulfonothioates prepared from cheap CD_3OD in two or three sequences. Finally, they are found to react with a number of aryl(hetero) iodides, boronic acids esters, and terminal alkynes, diazonium salts as well as β-ketoesters, and oxindoles as the coupling partners to assemble diversified C−SCD_3 bonds under mild reaction conditions (Figure 1c).

Two strategies for the preparation of *S*-(methyl-d_3) 4-methylbenzenesulfonothioate **3a** were successfully developed originally from CD_3OD, which was cheap, abundant (only 47 €/mol compare to 71 €/mol of d_6-DMSO and 2957 €/mol of CD_3I), and utilized as one of the most common deuterated solvents in NMR research (Figure 1a, right). First, $TsOCD_3$ **1**[11] can be obtained in one step on a 60 mmol scale after simple extraction and then directly subjected to the reaction with TsSNa **2a** in DMF on a 25 mmol scale, affording the desired compound **3a** in 95% yield with >99% purity and >99% incorporation under column-free purification (Figure 2).

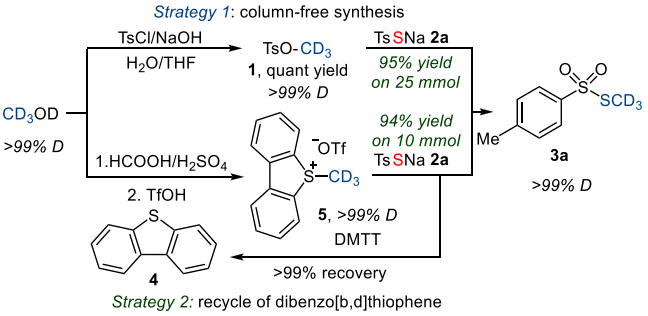


Figure 2. Two methods for preparation of reagent **3a** from commercial CD_3OD.

An alternative path includes the trideuteromethylation of **2a** with DMTT reagent,[7a] providing the product **3a** in 94% isolated yield. Meanwhile, >99% recovery of dibenzo[b,d]-thiophene **4** was also achieved; thus, this method represents a good example for sustainable synthesis. Compound **3a** is a white solid and stable at ambient temperature on the shelf for at least 6 months without detectable decomposition.

With this practical strategy in hand, a series of substrates on $ArSO_2SNa$ bearing Me **3a**; H **3b**; F **3c**, **3j**, **3m**; Cl **3d**, **3k**; CF_3 **3e**, **3i**; CN **3f**; and NO_2 **3g**, **3h** were investigated (Scheme 1). As a result, the corresponding products could be generated in good to excellent yields with >99% D incorporation. Naphthalene could be also applied to the current mild reaction conditions, and the product **3l** was obtained with high efficiency. In the case of the quinoline derivative, the coupled product **3n** was isolated in a slightly lower yield of 39% but with >99% D incorporation. Moreover, the structure of compound **3n** was first confirmed by X-ray analysis, and the strength of "S−S" bond was relatively weak, which was responsible for the high reactivity.

A nickel-catalyzed reductive cross coupling between reagent **3a** and aryl(hetero) iodides in MeOH was investigated in the presence of zinc as the reductant (Scheme 2).[12] After quick optimization of the reaction conditions between 4-iodoanisole **6a** and electrophilic SCD_3 reagent **3a** (for details, see the Supporting Information), we further explored the generality of this novel strategy to forge various C(sp^2)−SCD_3 bonds. In general, a variety of functional groups including OMe **6a**, Cl **6b**, CHO **6e**, COOMe **6f**, and NHAc **6i** were compatible with the current reaction conditions, and the corresponding products were obtained in moderate to good yields. Substrates containing OH **6c** and NH_2 **6d** smoothly reacted under extremely mild reaction conditions. Likewise, boronic acid ester and (pseudo)halide such as OTs group-containing **6g**, **6h** chemoselectively remained under the current reaction

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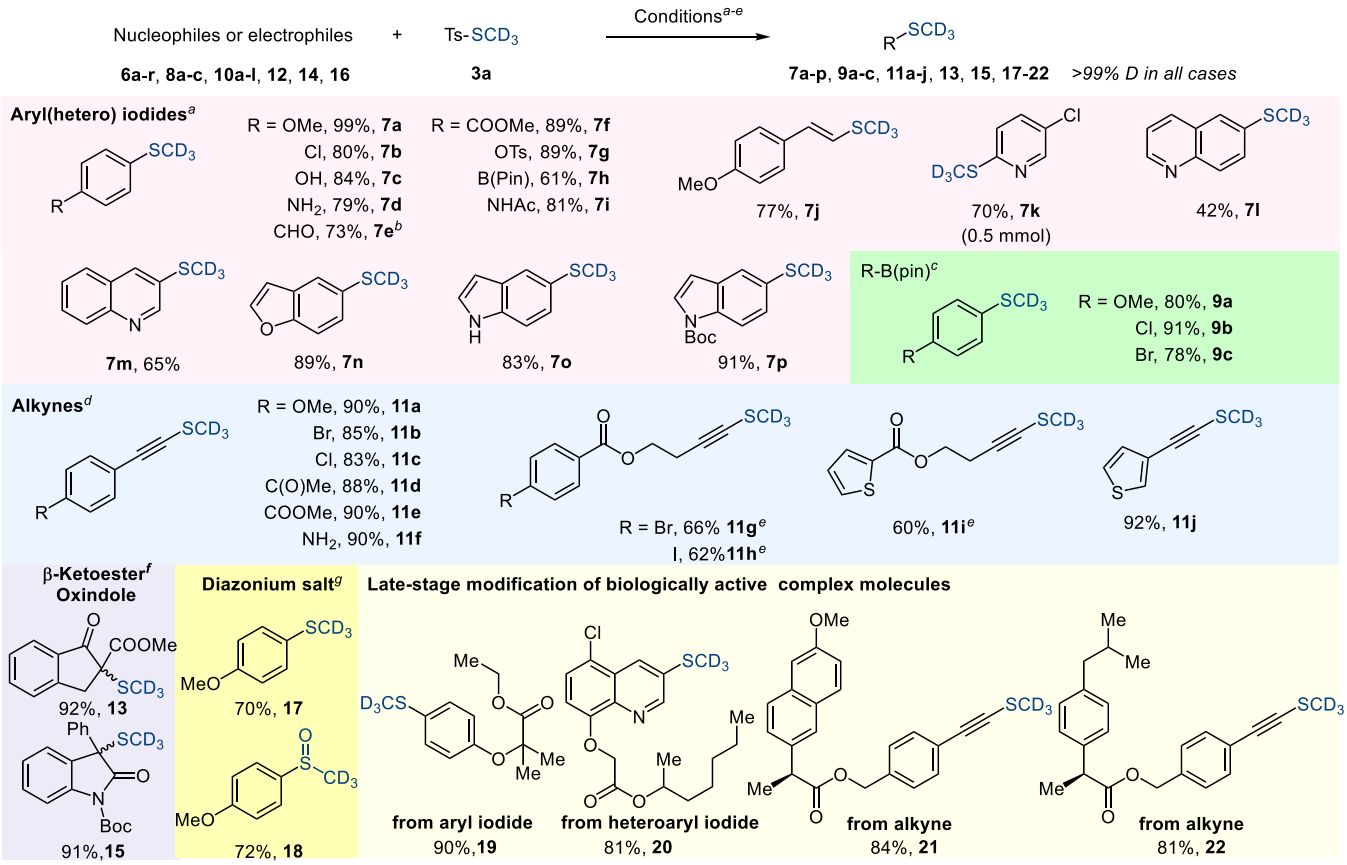
Scheme 2. Investigation of the Reactivity of Newly Prepared Reagent 3a



[a]**6a−r** (0.250 mmol), **3a** (1.50 equiv), $Ni(OAc)_2$ (0.0250 equiv), 2,2′-bipyridine (0.0300 equiv), and Zn (2.00 equiv) in MeOH (1.25 mL) at 60 °C for 2 h. [b]$Ni(OAc)_2$ (0.0500 equiv) and 2,2′-bipyridine (0.0600 equiv) were used. [c]**8a−c** (1.50 equiv), **3a** (0.500 mmol), $CuSO_4$ (0.0500 equiv), and $NaHCO_3$ (2.00 equiv) in MeOH (5.00 mL) at 22 °C for 24 h. [d]**10a−l** (0.500 mmol), **3a** (1.50 equiv), CuI (0.0500 equiv), Xantphos (0.0600 mmol), and K_2CO_3 (1.50 equiv) in DMSO (5.00 mL) at 22 °C for 24 h. [e]80 °C. [f]**12** or **14** (0.500 mmol), **3a** (2.00 equiv), and K_2CO_3 (2.00 equiv) in CH_2Cl_2 (2.50 mL) at 35 °C for 12 h. [g]**16** (0.500 mmol), **3a** (1.50 equiv), eosin Y (0.0500 equiv), and K_3PO_4 (2.00 equiv) in MeOH (2.50 mL) at 22 °C for 24 h in air or N_2. Isolated yields.

conditions, enabling the downstream orthogonal transformations. Pleasingly, our methodology could be further applied to more challenging vinyl iodide **6j** as well as heteroaryl derivatives including pyridine **6k**, quinoline **6l**, **6m**, benzofuran **6n**, indole **6o**, and Boc-protected indole **6p**, affording the final coupled products **7j−7p** in moderate to good yields. Boronic acid esters were also compatible under mild reaction conditions, furnishing the corresponding trideuteromethylthioesters **9a−9c** in reasonable yields with >99% D incorporation.

It was found that alkynes could efficiently participate in the coupling with the electrophilic SCD_3 reagent **3a** in the presence of K_2CO_3, a catalytic amount of CuI, and Xantphos. Delightedly, CuI-catalyzed trideuteromethylthiolation of the substrates containing OMe **10a**, Br **10b**, Cl **10c**, C(O)Me **10d**, COOMe **10e**, as well as primary amine **10f** was successfully conducted, leading to the formation of the corresponding trideuteromethylthioesters **10a−10f** in good to excellent yields with >99% D incorporation in all cases. For alkyl-substituted terminal derivates **10g−10i**, a slightly higher temperature (80 °C) was necessary to achieve higher conversion. Notably, a trideuteromethylthiolated scaffold was generated from thiophene-based alkyne in 92% yield with >99% D incorporation.

Direct trideuteromethylthiolation of *β*-ketoester and oxindole as the nucleophiles to construct C−SCD_3 bonds on a quaternary carbon center was rarely studied previously. To our delight, the trideuteromethylthioesters **13** and **15** could be obtained in very high yields with >99% D incorporation; thus, this mild transformation allowed for the development of potential enantioselective version in the presence of chiral reaction conditions. It was also discovered that the electrophilic reagent **3a** could also act as a radical acceptor when it was further subjected to the coupling of diazonium salts. The mild transformations were separately setup under N_2 or air atmosphere in the presence of eosin Y as the organic photosensitizer under Wang's reaction conditions.[8] As a result, the corresponding trideuteromethylthioester **17** and trideuteromethylated sulfoxides **18** were isolated as the final products in 70% and 72% yields, respectively. Meanwhile, the deuterated degree of >99% by employing the powerful electrophilic trideuteromethylthiolating reagent **3a** synthesized by our newly developed method was higher than previously reported (97% D incorporation in most cases).[8] Finally, a series of trideuteromethylthiolated derivatives of clofibrate **19**, cloquintocet-mexyl **20**, naproxen **21**, and ibuprofen **22** were isolated in good to excellent yields with >99% D incorporation, demonstrating the generality of this protocol.

To seek more insight on the relationship between the structure and reactivity, we selected 12 *S*-(methyl-d_3) arylsulfonothioates as the trideuteromethylthiolating reagents

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Org. Lett. 2022, 24, 6794−6799

to react with three kinds of substrates involving organic iodides, boronic acids, and terminal alkynes under the previously optimized conditions, and the results are summarized in Figure 3a,b. Interestingly, most of the *S*-

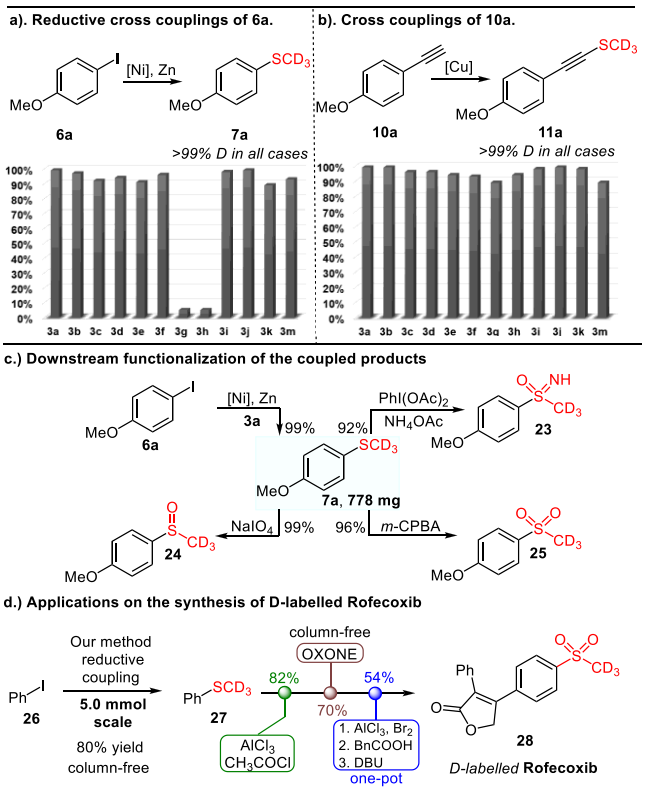

Figure 3. Structure and reactivity (SAR) study, downstream synthesis and synthetic applications. For detailed conditions, see the Supporting Information.

(methyl-d_3) arylsulfonothioates displayed similar reactivities toward the nickel-catalyzed reductive trideuteromethylthiolation. Both high yields and D incorporation level of the coupled products were achieved under previously optimized reaction conditions (Figure 3a). However, the reaction did not occur with full recovery of the 4-iodoanisole **6a** and the reagent **3g** bearing a nitro group **3f** and **3g** when they were located at different positions of the benzene ring (Figure 3a). It was proposed that the zinc dust could probably promote the reduction of nitro group.[13] In particular, good to excellent yields of the corresponding trideuteromethylthioesters were obtained when these selected reagents were subjected to the conditions of the copper-catalyzed cross coupling with terminal alkynes, representing a reliable and practical method to construct the C(sp^1)−SCD_3 bonds (Figure 3b). Therefore, the above results indicated that the sulfone's skeleton played a crucial role on the enhanced reactivity of these powerful electrophilic SCD_3 reagents.[14] Moreover, it provided more options for the direct synthesis of trideuteromethylthioesters, and we hope that development of the D-labeled drug discovery will benefit from such molecules containing trideuteromethylthiolated moieties in future.

To showcase the vast synthetic utility of our current methodology, modification of the biologically important subunit was explored (Figure 3c,d). Scale-up reactions of 4-iodoanisole **6a** were carried out, affording the corresponding trideuteromethylthioesters **7a** on 778 mg (Figure 3c). In the presence of $PhI(OAc)_2$ and $(NH_3)_2CO_3$, compound **7a** was successfully applied to the construction of sulfoximine **23** in 92% yield with >99% D incorporation. Oxidation of **7a** led to the formation of trideuteromethylated sulfoxide **24** and trideuteromethylated sulfone **25**, which were important scaffolds of sulfur in high valent states.[5k,15] The practicality and applicability of current methodology was next highlighted by the facile and rapid synthesis of D-labeled rofecoxib and firocoxib (Figure 3d). Column-free synthesis of trideuteromethylthioester **27** on a 5.0 mmol scale (80% yield) was achieved when the simple iodobenzene **26** was utilized as the coupling partner. Classic Friedel−Crafts acylation generated the ketone with high efficiency, and both of them could be used directly in the next transformations without further purifications. Treated by Oxone under aqueous conditions, trideuteromethylthioester could be converted into the corresponding trideuteromethylated sulfone which was not purified by silica gel chromatography. Then bromination and subsequent cyclization took place to give the final D-labeled rofecoxib **28** in acceptable yield.[16] Accordingly, D-labeled firocoxib could be prepared in only four steps from iodobenzene (for details, see the Supporting Information).

In summary, we developed a family of *S*-methyl-d_3 arylsulfonothioates and presented a powerful toolbox for direct trideuteromethylthiolation of a variety of suitable substrates including nucleophiles such as boronic acids esters, terminal alkynes, *β*-ketoester, oxindole, and diazonium salts. A first nickel-catalyzed reductive cross coupling between aryl(hetero) iodides and *S*-(methyl-d_3) 4-methylbenzenesulfonothioate was described. Moreover, all of the transformations were achieved with high efficiency, affording >99% D incorporation. Notably, electrophilic reactivity as well as radical ability of *S*-methyl-d_3 arylsulfonothioates was disclosed, and structure−reactivity relationship studies were also further explored. We believe this kind of easily accessible and useful trideuteromethylthiolating reagents will extend the space of deuteration and sulfur chemistry. Enantioselective trideuteromethylthiolation of *β*-ketoester and oxindole as well as other interesting reactions including mechanistic studies are currently being studied and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02680.

Details of experimental procedures, ^{1}H, ^{19}F, and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 2181808 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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