ORGANIC CHEMISTRY

Bioinspired design of a robust d_3-methylating agent

Minyan Wang*, Yunfei Zhao*, Yue Zhao, Zhuangzhi Shi†

Methods to incorporate deuterium atoms into organic molecules are valuable for the pharmaceutical industry. The introduction of deuterium atoms by a synthetic method enables the direct tracing of the drug molecule without substantially altering its structure or function. The methyl group is one of the most commonly occurring carbon fragments in biologically active molecules. Here, a biomimetic design reagent, 5-(methyl-d_3)-5*H*-dibenzo[*b*,*d*]thiophen-5-ium trifluoromethane sulfonate (DMTT), as an analog of *S*-adenosylmethionine (SAM), has been developed for the selective d_3-methylation of complex molecules bearing several possible reactive sites with excellent selectivity and high-level deuterium incorporation. A series of d_3-methylated organic molecules and deuterated pharmaceuticals were synthesized under the mild system with excellent functional group compatibility.

INTRODUCTION

The methyl group is the simplest organic substituent, yet it is not only important for synthetic and medicinal chemistry (*1*) but also plays a central role in a wide range of biological processes, including DNA replication, protein modification, lipid biosynthesis, and various other metabolic pathways (*2*–*5*). Most biological methylation uses members of the *S*-adenosylmethionine (SAM) superfamily, commonly known as radical methyltransferases, in which SAM is selectively cleaved by its C—S bond under the reaction with various nucleophiles to generate stable *S*-adenosyl-L-homocysteine, leading to the methylation of complex molecules such as nucleic acids, proteins, and natural products in a S_N2 manner (Fig. 1A) (*6*–*7*). Inspiration by SAM, Baran and coworkers (*8*) developed an elegant methylating agent, zinc bis(phenylsulfonylmethanesulfinate), for the methylation of heteroarenes. Very recently, other methylating reagents such as 1,1-diborylmethane (*9*), α-iodosulfones (*10*), trimethylphosphate (*11*), 1-methoxy-2,2,6,6-tetramethylpiperidine (TEMPO-Me) (*12*), MeZnCl (*13*), Lewis base BH_3/DMF (*14*), and $[Me_2Cl][Al(OTeF_5)_4]$ (*15*) exhibit unique reactivity during the research of methylation. Despite these notable advances, the corresponding d_3-methylation has not been well developed.

Deuterium atoms can be used as tracer atoms to elucidate metabolic pathways in medicinal chemistry (*16*). Owing to the higher bond dissociation energy than the C—H bond, the incorporation of deuterium can impart marked improvements to drug candidates, related to absorption, distribution, and metabolism in organisms (*17*). Numerous efficient strategies of deuterium labeling techniques have been developed recently including direct H/D exchange (*18*–*19*), dehalogenative deuterium mediated by transition metal catalysis (*20*), bases (*21*–*22*), or radicals (*23*), and so on (*24*–*25*). A substantial number of deuterium-labeled drug candidates have been synthesized and submitted to clinical trials in the past few decades (*26*–*27*). Austedo with two OCD_3 groups, as a treatment for symptoms of Huntington's disease, was finally approved by the U.S. Food and Drug Administration in 2017 as the first deuterated drug (Fig. 1B) (*28*). In general, the d_3-methylated group incorporation significantly affected the ADME (absorption, distribution, metabolism, and excretion)–related processes and attenuated metabolism of certain pharmacologically active compounds (*29*–*30*). From the viewpoint of synthetic chemistry, d_3-methylation is the most ideal approach because it has the capability to directly introduce the D-labeled methyl group into structurally diverse molecules (*31*–*33*). Because of the presence of multiple nucleophilic sites in a complex molecule with subtle differences in the activation barriers, controlling the positional selectivity represents a key challenge. Traditionally, CD_3I (*34*), $(CD_3)_2SO_4$, and CD_3OD have been widely used as deuterium methylating reagents, albeit with volatility, corrosion, toxicity, and carcinogenicity concerns (*35*–*36*). However, these highly reactive reagents usually lead to poor chemoselectivity and overmethylation. Reductive deuteriation of carboxylic acids (*37*), amides (*38*), and nitriles (*39*–*41*) provides protocols to incorporate d2-methyleneation. Nevertheless, the invention of a reagent to accomplish direct, scalable, and predictably selective d_3-methylation under mild and environmentally friendly conditions is in high demand. Umemoto's reagent is a commercially available and widely used electrophilic trifluoromethylating agent (*42*). Bioinspired by the reactivity of SAM, together with the design principle of Umemoto's reagent, we report herein the invention of **DMTT** (5-(methyl-d_3)-5*H*-dibenzo[*b*,*d*]thiophen-5-ium trifluoromethane sulfonate) (*43*), a d_3-methylating agent using the dibenzo[*b*,*d*]thiophene framework to simplify the SAM structure, successfully blending high reactivity and selectivity with a safety profile that is particularly attractive for medicinal and pharmaceutical chemistry (Fig. 1C). **DMTT** could be simply prepared from dibenzo[*b*,*d*]thiophene (*44*–*45*) and CD_3OD in 91% yield on a large scale, and the compound is very stable when stored as a solid at ambient temperature. Significantly, the d_3-methylation of **DMTT** with substrates proceeds in a biomimetic process, thus exhibiting excellent chemoselectivity under extremely mild conditions analogous to SAM chemistry in a living organism.

RESULTS

Reaction condition optimization

Trideuteromethylation of carboxylic acids is ubiquitously used in chemical research. Initially, we chose the carboxylic acid **1a** with a carboxyl and a *N*,*N*-dimethyl group to check the reactivity and selectivity of the **DMTT** agent (Table 1). Compared to the NMe_2 substituent, the carboxylic group preferentially reacted with **DMTT**, forming the desired d_3-methylation product **1b** in 90% isolated yield with deuterium retained completely in the presence of K_2CO_3 (entry 1). This d_3-methylation process cannot proceed in the absence

State Key Laboratory of Coordination Chemistry, Chemistry and Biomedicine Innovation Center (ChemBIC), School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, China.
*These authors contributed equally to this work.
†Corresponding author. Email: shiz@nju.edu.cn

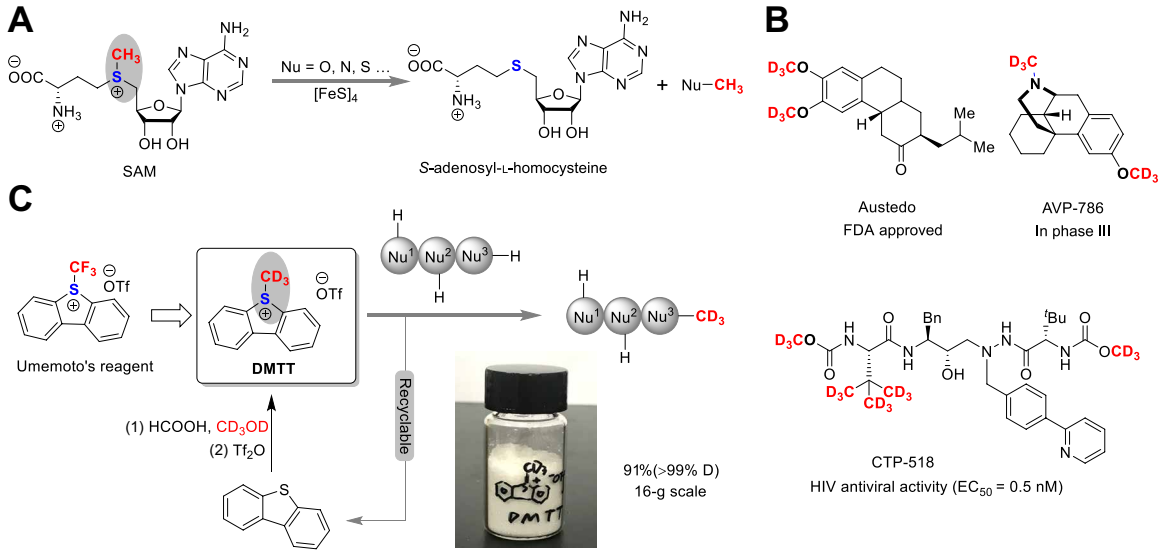
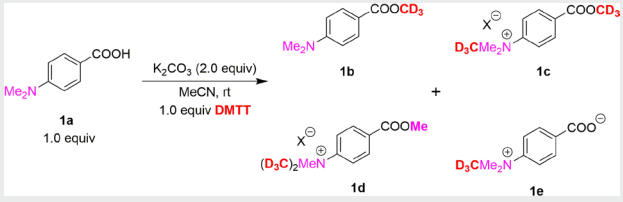


Fig. 1. Bioinspired invention of DMTT as a robust d_3-methylating agent. (**A**) SAM methyl transferase mediated nucleophilic reactions. (**B**) Deuterium-labeled drugs and candidates. (**C**) Invention of d_3-methylating reagent **DMTT**. Reaction conditions: (1) HCOOH (3.0 equiv, 88 wt % aqueous solution), CD_3OD (10.0 equiv, >99% D), H_2SO_4 (11.0 equiv, 98 wt %), reflux at 60°C for 4 hours to afford methyl-d_3 formate; (2) dibenzothiophene (1.0 equiv), and above methyl-d_3 formate, heat up to 60°C until the mixture became a clear solution. Photo credit: Yunfei Zhao, Nanjing University. EC_{50}, half median effective concentration.

Table 1. Reaction development. Reaction conditions: **1a** (0.2 mmol), **DMTT** (0.2 mmol), and base (0.4 mmol) in 2 ml of MeCN for 12 hours.



Entry	Variation from the standard conditions	1b/1c/1d/1e*
1	None	90 (99% D) †/0/0/0
2	Without K_2CO_3	0/0/0/0
3	Using KOH	35 (99% D)/0/0/0
4	Using DBU	50 (99% D)/16/0/0
5	1.5 equiv of DMTT	62 (99% D)/20/0/0
6	CD_3I (1.0 equiv.) instead of **DMTT**	2/0/0/8
7‡	CD_3I (5.0 equiv) instead of **DMTT**	7/0/43/10
8	$(CD_3)_2SO_4$ (1.0 equiv) instead of **DMTT**	31/27/0/0
9	DMSO-d_6 instead of **DMTT**	0/0/0/0
10	$[CD_3Ph_2S]^+OTf^-$ instead of **DMTT**	64/0/0/0

*^{1}H NMR yields were presented using CH_2Br_2 as an internal standard. †Isolated yield. ‡At 80°C.

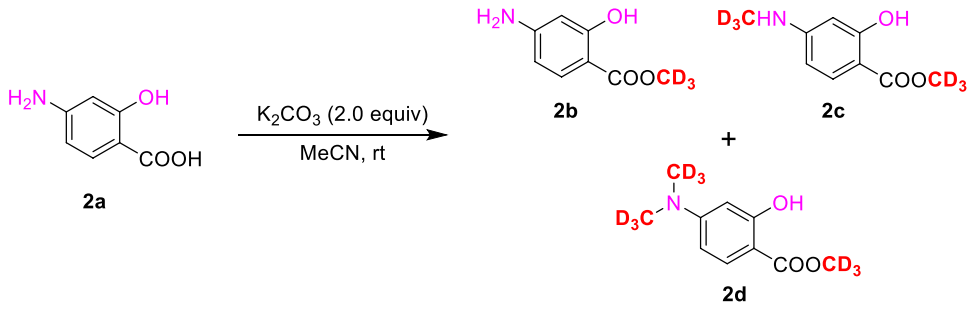
of base (entry 2). Screening of other bases did not provide higher yields (entries 3 and 4). When increasing the amount of **DMTT** to 1.5 equiv, the overmethylation product **1c** was formed in 20% yield (entry 5). Using CD_3I as the deuterium source led to a different chemoselectivity. Using 1.0 equiv of CD_3I proved to prefer quaternization of *N*,*N*-dimethyl group (entry 7), and a larger excess of CD_3I generated a by-product **1d** with CD_3/CH_3 exchange (entry 7). In addition, the selection of $(CD_3)_2SO_4$ provided the desired product **1b** in a much lower efficiency with 27% yield of by-product **1c** (entry 8). These results indicate that **DMTT** exhibited significantly different reactivity from CD_3I and $(CD_3)_2SO_4$ depending on the different sterically hindered leaving groups. In addition, other sulfur-based reagents were also examined. Dimethyl sulfoxide (DMSO)–d_6 cannot promote the methylation-d_3 process under our developed conditions (entry 9), while the reagent $[CD_3Ph_2S]^+OTf^-$ was proved to be less effective (entry 10).

On the basis of the tested conditions, 1.0 equiv of **DMTT** furnished the desired methyl-d_3 esterification product in excellent yield and suppressed the generation of by-products. To further illustrate this selectivity, substrate **2a** with three nucleophilic sites was treated with **DMTT** under the above conditions (Fig. 2). To our delight, compound **2a** reacted with **DMTT** also tends to form the esterification product **2b** in 76% yield. Again, treatment of CD_3I and $(CD_3)_2SO_4$ with **2a** under the same conditions showed poor selectivity. Therefore, **DMTT** should be used as a very important, predictable, and reliable reagent for trideuteromethylation.

DISCUSSION

Application in late-stage modification and deuterated drug synthesis

Following identification of the optimized d_3-methylation with **DMTT** under developed mild conditions, various nucleophilic reagents bearing several possible reactive sites were examined (Table 2). Notably, the substrates with tertiary alcohol hydroxyl (**3a**) and amino (4a) groups were well tolerated. The reaction showed excellent selectivity for esterification (**3**-**4b**), in which alcohol elimination and *N*-methylation byproducts were not observed. When indole **5a** was used, the esterification product **5b** was obtained in 84% yield with



	2b	2c	2d
DMTT (1.0 equiv)	76% (99% D)	2%	0%
CD_3I (1.0 equiv)	12%	9%	6%
$(CD_3)_2SO_4$ (1.0 equiv)	65%	8%	4%

Fig. 2. Investigations of compound 2a with DMTT agent. Reaction conditions: **2a** (0.2 mmol), DMTT (0.2 mmol), and base (0.4 mmol) in 2 ml of MeCN for 12 hours, ^{1}H NMR yields were presented using CH_2Br_2 as an internal standard. rt, room temperature.

the N—H bond preserved. α-Amino acid **6a** was also suitable for d_3-methylation, resulting in 89% yield (**6b**). Numerous pharmaceuticals and natural products were also investigated, and various d_3-methylated biomolecules were generated in good to excellent yields. As an important immune inhibitor, mycophenolic acid (**7a**) with multiple hydroxyl groups also reacted smoothly with sole selectivity. The carboxylic acid preferentially reacted with **DMTT** in the presence of hydroxyl groups and showed excellent selectivity (**8b**-**12b**) under practical mild conditions, avoiding the formation of intermolecular esterification and overmethylation using traditional CD_3 reagents. When substrates had oxoimidazolidine and tetrahydrothiophene motifs, d_3-methylation reacted exclusively at the carboxylic acid group (**13b**) in 65% yield with 99% D incorporation. Furthermore, oligopeptides were tested under standard conditions; **14b** and **15b** were obtained in 92 and 48% yields, respectively. Among the substrates, the reactions of **12a** and **14a** with **DMTT** were conducted on a gram scale without the loss of the yield or selectivity.

Next, the phenols, which have higher pK_a (where K_a is the acid dissociation constant) values than the corresponding carboxylic acids, were also investigated. The phenols containing hydroxyl (**16b**), indole N—H (**17b**), amine (**18b**), and amide (**19b**) substituents were well compatible, with excellent selectivity. The drug molecules **20**-**21a**, which have sensitive functional groups, including 2-azetidinone, aliphatic hydroxyl, and terminal alkynyl frameworks, could be late stage modified by **DMTT** at the phenolic hydroxyl selectively, and the products **20**-**21b** were generated on a gram scale without notable decreases in yields (95 to 96%) or selectivity. The structure of **21b** was also determined by x-ray crystallographic analysis. Notably, for the reaction of **DMTT** with (+)-ascorbic acid (**22a**), the two aliphatic hydroxyl groups were also tolerated, and two phenol ether groups were preferentially produced, generating product **22b** in 91% yield. Trideuteromethylation of pyridoxine (**23a**) formed the desired product **23b** in 83% yield, and side reactions such as pyridine *N*- and alcohol *O*-methylation were completely inhibited.

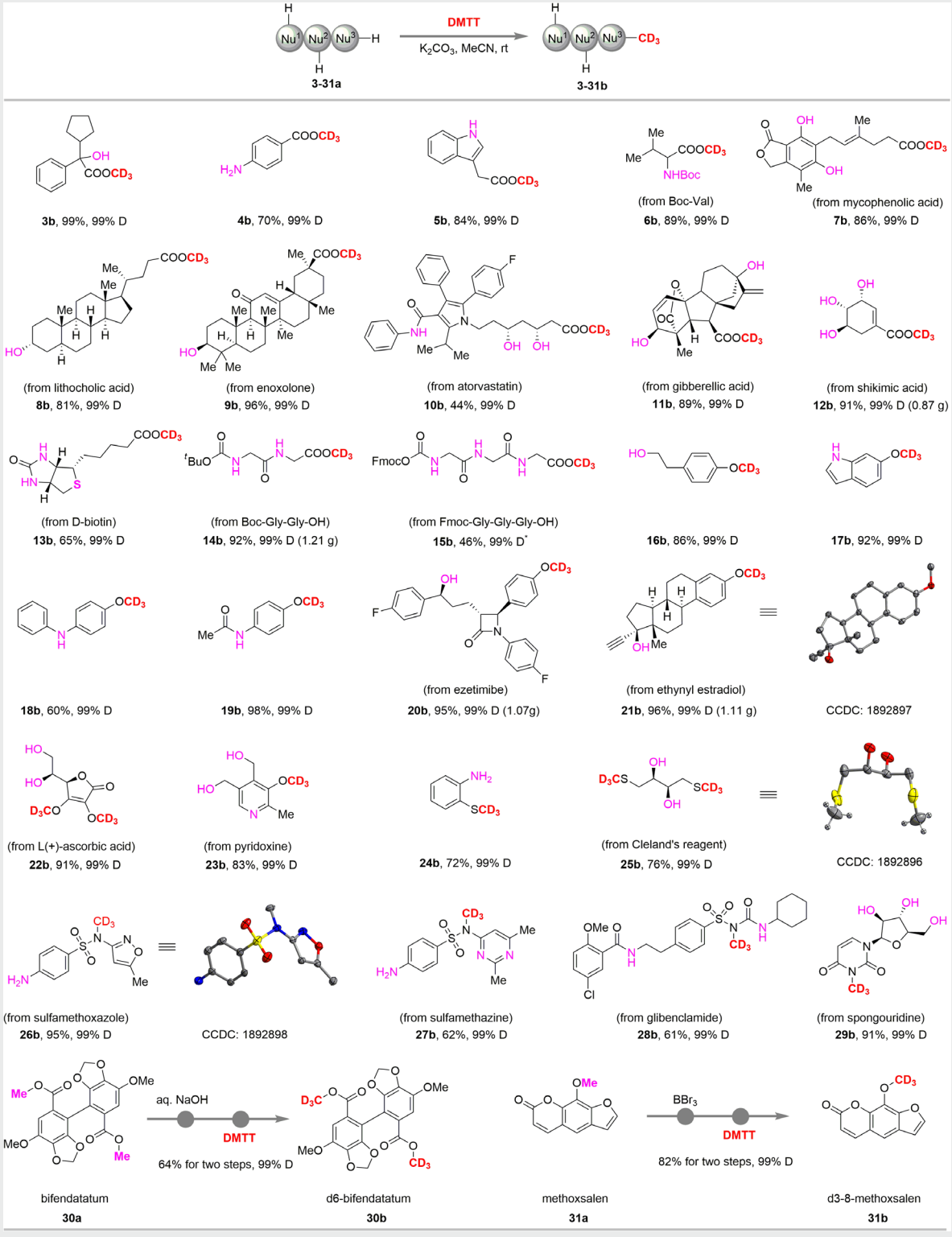
In addition, **DMTT** was compatible with many common biologically active functional groups. When 2-aminobenzenethiol (**24a**) is used, only S atom d_3-methylation (**24b**) is observed. Cleland's reagent bearing two mercapto and two hydroxyl groups is used as a reducing or "deprotecting" agent for thiolated DNA (*46*), and it can undergo selective d_3-methylation with **DMTT** at the mercapto group, leading to product **25b** in 76% yield. Using sulfonamides **26**-**28a** as substrates having amino and amide substituents, the reaction of **DMTT** shows excellent selectivity for the sulfonamide NH group, in which the N—H bond connected to the sulfone group has the lowest pK_a value. Last, spongouridine **28a** bearing three hydroxyl groups was also tested with **DMTT**, and the NH d_3-methylated compound **29b** was obtained in 91% yield with excellent deuterium incorporation. Among the products, the molecular structures of **25**-**26b** were confirmed by x-ray analysis. In the presence of K_2CO_3, the methylation-d_3 took place selectively on the carboxylic acids, phenols, and thiols with their NH_2, NH, and alkyl-OH intact. The order of reactivity in increasing order is amines and alkyl-OH < phenols < carboxylic acids. In particular, *N*-methylated-d_3 products were only observed when the NH connected with strong electron-withdrawing groups, such as *N*-sulfonyl or *N*,*N*-diacetyl groups.

H/D exchange at the C—H bonds of the precursors is a common method for the preparation of deuterium-labeled drug molecules (*31*). However, highly efficient and regioselective H/D exchange of a methyl group in a complex molecule remains challenging. With the **DMTT** reagent in hand, we can provide a reliable route to convert commercially available drugs to the corresponding d_3-deuterated variants. For example, bifendatatum (**30a**), an antihepatitis drug, was hydrolyzed to form a carboxylic acid intermediate and then underwent d_3-methylation with **DMTT**, producing the d_3-bifendataum (**30b**) with high-level deuterium incorporation. Methoxsalen (**31a**) is a commercial drug used to treat psoriasis, eczema, vitiligo, and some cutaneous lymphomas in conjunction with exposing the skin to ultraviolet A light from lamps or sunlight. This substrate was demethylated in the presence of BBr_3 and subsequently reacted with **DMTT** to generate d_3-methoxsalen (**31b**) in 82% yield.

Application in Ni-catalyzed dimethylation-d_6 of amines

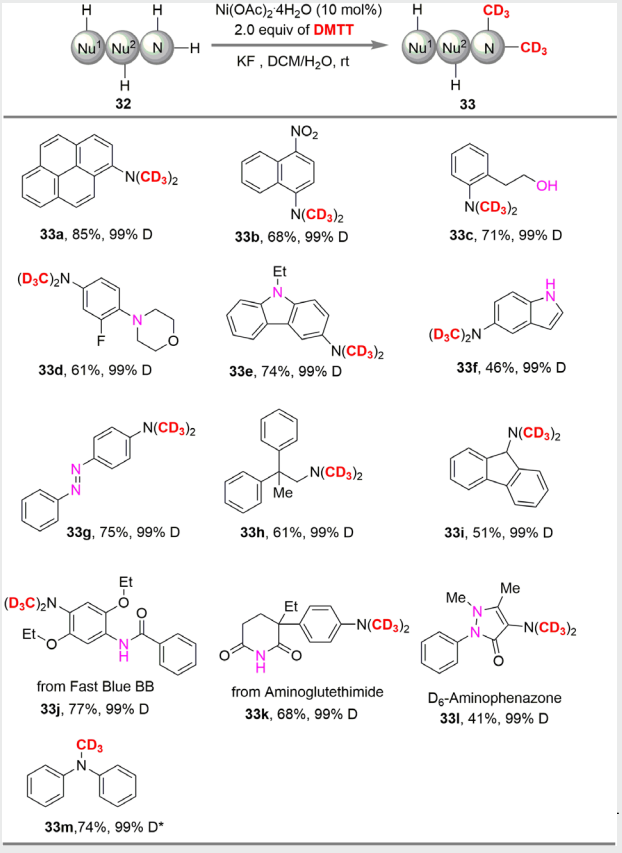
The direct methylation of a primary amine with methyl iodide (*47*) is usually not a feasible method for the preparation of secondary amines since overmethylation occurs to form quaternary ammonium salts. To further investigate the superiority of **DMTT**, dimethylation of primary amines was carried out smoothly in the presence of 10 mol% $Ni(OAc)_2{\cdot}4H_2O$, leading to the *N*,*N*-dimethyl-d_3 products

Table 2. Substrate scope, late-stage modification, and deuterated drug synthesis. Reaction conditions: substrates **a** (1.0 equiv), **DMTT** (1 to 2 equiv), and K_2CO_3 (2 to 4 equiv) in 2 ml of MeCN for 12 hours. Isolated yields were presented.



*Reaction conditions: substrates **a** (1.0 equiv), **DMTT** (1.0 equiv), and KOH (2.0 equiv) in 2 ml of MeCN/H_2O (v:v = 1/1) for 12 hours. Isolated yields were presented.

Table 3. Dimethylation-d_6 of primary amines. Reaction conditions: substrates **32** (1.0 equiv), **DMTT** (2 equiv), $Ni(OAc)_2{\cdot}4H_2O$ (10 mol%), and KF (2 equiv) in 2 ml of DCM/H_2O (v:v = 20/1) for 12 hours. Isolated yields were presented.



*1.0 equiv of **DMTT** was used.

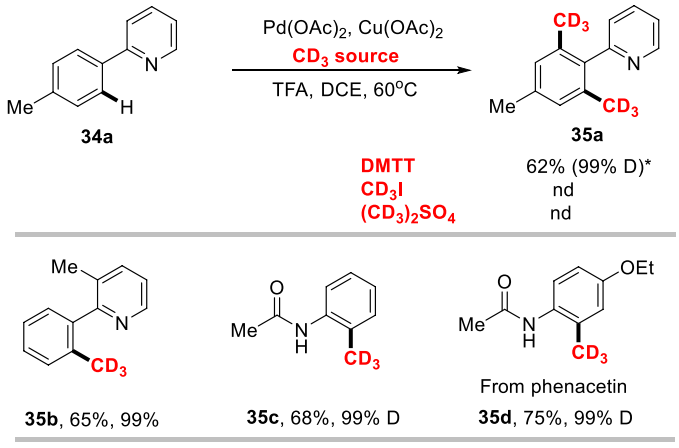


Fig. 3. Pd-catalyzed C—H bond methylation-d_3. Reaction conditions: substrates **34** (1.0 equiv), **DMTT** (3.0 to 1.2 equiv), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (1.2 equiv), and trifluoroacetate (TFA) (5.0 equiv) in 2 ml of dichloroethane (DCE) for 12 hours at 60°C. Isolated yields were presented. *3.0 equivalents of **DMTT** were used. nd, not detected.

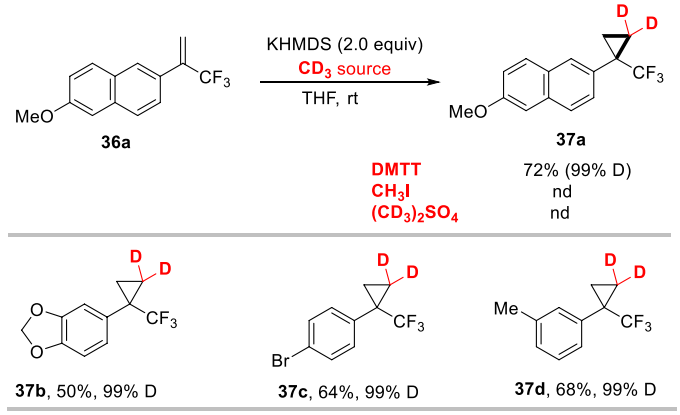


Fig. 4. Methyleneation of trifluoromethyl-substituted alkenes. Reaction conditions: substrates **36** (1.0 equiv), **DMTT** (2.0 equiv), and KHMDS (2.0 equiv) in 2 ml of tetrahydrofuran (THF) for 12 hours at room temperature. Isolated yields were presented.

in modern to good yields (Table 3). Compared with these developed approaches, **DMTT** showed excellent selectivity under mild conditions, and the overmethylation quaternary ammonium salts did not observe. The hydroxyl group is compatible in this system to deliver **33c** in 71% yield with 99% D incorporation. The aryl amines containing other dialkylamino groups, such as **33d** and **33e**, are also well tolerated to furnish the corresponding methylation-d_3 products in 61 and 74% yield, respectively. When the substrate **32f** with active amino group was treated with **DMTT** under standard conditions, the **33f** was isolated in 46% yield with active amino intact. The reaction of alkyl amines with **DMTT** gave the corresponding methylation-d_3 products in moderate yields. What is more, the functional molecules with amines groups (**33j** and **33k**) were also investigated. Using the developed method, the d_6-aminophenazone **33l**, as important antipyretic analgesics, could be easily be synthesized from the available 4-aminoantipyrine **32l**. Last, the secondary amines such as diphenylaniline **32m** can also be easily d_3-methylated in the presence of nickel catalyst affording the *N*-(methyl-d_3)-*N*-phenylaniline **33m** in 74% yield.

Application in C—H bond activation and d_3-methylation

DMTT has also played an important role in the transition metal-catalyzed C—H bond activation (Fig. 3) (*45*). Using pyridyl as directing group, the *ortho*-methylation-d_6 was achieved in the presence of palladium catalyst, leading to the dimethylation-d_6 product **35a** in 62% isolated yield with 99% D value. In the same condition, CD_3I and $(CD_3)_2SO_4$ failed to accelerate the methylation process. Increasing the steric hindrance of directing group and reducing the loading of **DMTT**, the *ortho*-monomethylation-d_3 product **35b** was observed without any deuterium loss. Using acetylamino as directing group, monomethylation-d_3 was detected in the presence of 1.2 equivalents of **DMTT** under standard condition, whereas only trace amount of *ortho*-bismethylation-d_3 was observed. The drug molecules were also modified using the developed palladium catalyzed C—H bond methylation-d_3. Phenacetin, which was used to treat fever, headache, and neuralgia, can be methylated-d_3 smoothly to change pharmacological activity and avoid some side effects, leading the methyl-d_3 phenacetin **35d** in 75% yield with 99% deuterium incorporation.

Application in d2-methyleneation of cyclopropanes

In addition to a d_3-methylating agent, **DMTT** also showed the intrinsic reactivity of a sulfur ylide (Fig. 4). For example, in the presence of strong base, **DMTT** underwent deprotonation to afford methylene intermediate, which captured by trifluoromethyl substituted alkenes **36** to furnish the deuterated cyclopropanes **37** under mild conditions. Various aryl substituted cyclopropanes were obtained in the yields of 50 to 72%, which provide a powerful evidence to prove the widely application value of **DMTT**.

CONCLUSION

In conclusion, we have developed a new d_3-methylating reagent, **DMTT**, and applied it in the many methylation processes, serving as a powerful approach to install deuterium in organic molecules and providing a new diagnostic tool in drug development. The advantage of this transformation is the simple experimental protocols, excellent selectivity, and high-level deuterium incorporation. We believe that this strategy will be used in drug modification in the pursuit of new deuterated therapeutics.

MATERIALS AND METHODS

General information

Unless otherwise noted, all the reaction was performed under air atmosphere. All new compounds were fully characterized. ^{1}H, ^{13}C, and ^{19}F nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III 400 or 500 MHz spectrometer. ^{1}H NMR spectra data were reported as δ values in parts per million relative to $CDCl_3$ (δ = 7.26), CD_3CN (δ = 1.94), CD_3OD (δ = 3.31), or DMSO-d_6 (δ = 2.50). ^{13}C NMR spectra data were reported as δ values in parts per million relative to $CDCl_3$ (δ = 77.00), CD_3CN (δ = 118.30), CD_3OD (δ = 49.15), or DMSO-d_6 (δ = 39.52). Mass spectra were conducted at Micromass Q-Tof instrument electron spray ionization (ESI) and Agilent Technologies 5973N electron ionization (EI). Infrared spectra were recorded on a Fourier transform infrared spectrometer. All materials obtained from commercial suppliers were used without further purification.

General procedure for synthesis of trideuteromethyl reagent DMTT

According to our patent (*43*), to a 50-ml round flask was added formic acid (7.8 ml, 150 mmol, 3 equiv, 88 wt % aqueous solution), CD_3OD (20.2 ml, 500 mmol, 10 equiv, d = 0.89 g/ml, 99% D). Then, sulfuric acid (8.8 ml, 165 mmol, 11 equiv, 98%) was added dropwise to the above solution with stirring. The reaction was heated at 60°C and stirred for 4 hours. The methyl-d_3 formate containing a small amount of deuterated methanol was directly distilled at atmospheric pressure (33° to 38°C). The methyl-d_3 formate was used without further purification.

A 50-ml round flask was charged with dibenzothiophene (9.2 g, 50 mmol, 1 equiv) and above distilled methyl-d_3 formate. The mixture was stirred at 0°C, and Tf_2O (20 ml) was added dropwise with stirring. Then, the reaction was heated up to 60°C. When the mixture became a clear solution, the reaction was poured into water (100 ml), extracted with CH_2Cl_2 (50 ml × ȝ3), dried with $MgSO_4$, and concentrated in vacuo. The obtained crude product was washed with Et_2O (50 ml × ȝ3) and dried under vacuum to afford the trideuteromethyl reagent DMTT (16.0 g, 91%, 99% D).

General procedure for synthesis of 3b-31b

Carboxylic acid **a** (0.2 mmol, 1.0 equiv), **DMTT** (0.2 to 0.4 mmol, 1 to 2 equiv), K_2CO_3 (0.4 to 0.8 mmol, 2 to 4 equiv), and MeCN (2 ml) were added to a Schlenk tube. The reaction was stirred at room temperature for 12 hours. Then, the resulting mixture was concentrated in vacuo, and the residue was purified by column chromatography to afford the corresponding product b.

General procedure for synthesis of 33a-33 l

$Ni(acac)_2$ (0.02 mmol, 0.1 equiv), amines (0.2 mmol, 1.0 equiv), potassium fluoride (KF) (0.4 mmol, 2.0 equiv), **DMTT** (0.4 mmol, 2.0 equiv), and dichloromethane (DCM)/H_2O (2 ml, v:v = 20:1) were added to a 25-ml Schlenk tube. The reaction was stirred at room temperature for 12 hours. Then, the resulting mixture was concentrated in vacuo, and the residue was purified by column chromatography to afford the corresponding products 33.

General procedure for synthesis of 35a-35d

$Pd(OAc)_2$ (0.02 mmol, 0.1 equiv), **34** (0.2 mmol, 1.0 equiv), $Cu(OAc)_2$ (0.24 mmol, 1.2 equiv), **DMTT** (0.24 to 0.6 mmol, 1.2 to 3.0 equiv), trifluoroacetate (TFA; 1.0 mmol, 5.0 equiv), and dichloroethane (DCE; 2 ml) were added to a 25-ml Schlenk tube. The reaction was stirred at 60°C for 12 hours. Then, the resulting mixture was concentrated in vacuo, and the residue was purified by column chromatography to afford the corresponding products **35**.

General procedure for synthesis of 37a-37d

36 (0.2 mmol, 1.0 equiv), **DMTT** (0.4 mmol, 2.0 equiv), potassium bis(trimethylsilyl)amide (KHMDS) (0.4 mmol, 2.0 equiv), and tetrahydrofuran (THF; 2 ml) were added to a 25-ml Schlenk tube. The reaction was stirred at room temperature for 12 hours. Then, the resulting mixture was concentrated in vacuo, and the residue was purified by column chromatography to afford the corresponding products **37**.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/6/19/eaba0946/DC1

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