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Broadening of Horizons in the Synthesis of CD$_3$-labeled Molecules

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In the light of the recent potentials of deuterated molecules as pharmaceuticals or even in mechanistic understanding, efficient methods for their synthesis are continually desired. CD$_3$-containing molecules are prominent amongst these motifs due to the parallel of the "magic methyl effect": introducing a methyl group into pharmaceuticals could positively affect biological activities. The trideuteromethyl group is bound to molecules either by C, N, O, or S atom. For a long time, the preparation methods of such labeled compounds were underestimated and involved multi-step syntheses. More recently, specific approaches dealing with the direct incorporation of the CD$_3$ group have been developed. This Review gives an overview of the methods for the preparation of CD$_3$-labeled molecules from conventional functional group interconversion techniques to more direct catalytic approaches and include radical strategy. Detailed reaction mechanisms are also discussed.

Introduction

In medicinal chemistry, a bioisostere is a molecule resulting from the exchange of an atom or of a group of atoms with an alternative, broadly similar, atom or group of atoms. The concept of a bioisosteric replacement is to prepare a new molecule with updated biological properties – while engaging only small modifications from the parent compound– in order to lower the toxicity, alter pharmacokinetics, and enhance the desired biological or physical properties. Among the bioisosteric replacements, the switch of hydrogen by deuterium "heavy hydrogen" is the most conservative affording a minor impact on the physicochemical properties, but it can induce a significant modulation of the metabolism. This action mode is based on the kinetic isotope effect: when the C–H bond breaking occurs during an important step of the metabolism process, the degradation of deuterated drugs occurs more slowly. For instance, the deuteration of Venlafaxine (SDZ-254), an antidepressant within SNRI class of medications, reduces the rate of metabolism by 50% in vitro (Figure 1). While chemists have been using deuterium for decades to tweak medicinal compounds and improve their pharmacokinetic and toxicity profiles, it is only in 2017 that the first deuterated drug Austedo® for the treatment of
Huntington's cholera was approved by the US Food and Drug Administration (FDA) and went to the market. The switch from OMe to OCD$_3$ groups enables to slower the Austedo's clearance down, giving a dosage advantage. Besides boosting drug half-lives, the introducing deuterium group can also help to stabilize chiral centers of a drug, avoiding racemization such as in deuterated Thalidomide. A handful of deuterated compounds, including those containing CD$_3$ groups instead of CH$_3$ groups (Figure 1), are now in the clinic for various indications. It should be noted that this strategy does not always pay off; for example, CTP-499, a lead deuterated drug developed by Concert Pharmaceuticals, was wiped out in clinical trials (Figure 1).

Figure 1. Examples of CD$_3$-Containing Molecules in Drug Designs.

The improvement of drugs wrought by the switch of hydrogen by deuterium has prompted chemists to innovate in deuteration methods. In contrast to methylation, which is covered by several reviews or D-labeling molecules by H-D exchanges, the synthesis of CD$_3$-labeling molecules, has been less subject to overview reviews. Although the literature abounds in examples of the synthesis of CD$_3$-containing molecules, no specific methodology dealt exclusively with incorporating the CD$_3$ unit, recent examples aside. In most cases, methylation strategies were upgraded toward trideuteromethylation with one or a couple of examples. Besides, the current chemical search tools are not convenient to handle isotope-labeled molecules. This Review aims to provide a critical overview of the progress that has been made towards a general solution to incorporate the CD$_3$ unit into organic molecules, ranging from reduction method to cross-coupling reaction and more recent developments (radical photoredox chemistry). The sections of this Review are organized by reaction bond that is created (i.e., CD$_3$–C, CD$_3$–N, CD$_3$–O, and CD$_3$–S) and by which type of reaction is employed to create them. For the construction of C–CD$_3$ bond, there are six main approaches: i) by reduction using deuteride sources; ii) H/D exchanges; iii) electrophilic addition using (surrogate) trideuteromethylation agent; iv) transition-metal-catalyzed cross-coupling reactions; v) C–H bond trideuteromethylation; vi) radical reactions (Figure 2a). The N–CD$_3$ linkages are often prepared by i) reduction of carbamates, ii) H/D exchanges of methylamine or iii) by N–trideuteromethylation (Figure 2b). The O–CD$_3$ or S–CD$_3$ units can be generated by either trideuteromethylation reaction or O or S bond formations (Figure 2c and d). Therefore, deuterium sources can be categorized into three main groups the deuteride sources (Figure 2E), he electrophilic trideuteromethylation reagents (Figure 2F) and the nucleophilic trideuteromethylation reagents or trideuteromethylated radical precursors (Figure 2G). This discussion of innovative strategies developed for various CD$_3$X-containing molecules should provide chemists with a set of resources and conditions applicable to a range of challenging substrates, including potential pharmaceuticals or agrochemicals.
1. Organic Molecules Containing C–CD$_3$ Bond

The carbon-carbon bond formation is the core of organic synthesis. The C-methylation methods are well-developed that include both designs of methylation reagents and protocols. In contrast, methods to link a trideuteromethyl group to organic molecules by C atom are currently under development. The most classical approaches involve H-D exchanges at acidic positions or multi-step methods based on the uses of deuterated reducing reagents. More recently, methods for direct trideuteromethylation have been reported using (surrogate) deuterated iodomethane or radical pathways.

1.1. Reductive Methods

Conventional functional group interconversion is a traditional way to synthesize CD$_3$-bearing molecules. It is generally achieved via a deuterated reduction of appropriate starting materials. Several methods and applications have been reported in the literature. We selected the preparation of SD-560, idiopathic pulmonary fibrosis (IPF) drug, to illustrate this chemistry. In recent years, Auspex Pharmaceuticals and Concert Pharmaceuticals have developed two pathways to convert the 5-substituent on the pyridine to the 5-CD$_3$ group (Scheme 1). In the first pathway, the carboxylic acid function of the pyridinone is converted to the CD$_3$ moiety via a sequence of anhydride formation, NaBD$_4$-mediated reduction, bromination, and LiAlD$_4$-mediated Br-D exchange (Scheme 1, top). In the second pathway, the reduction of the nitrile group was achieved using highly flammable deuterium gas (D$_2$) in the presence of Pd/C as catalyst to afford 5-(methyl-d$_3$)pyridin-2-ol, which is latter transformed into SD-560 by Cu-catalyzed N-arylation with iodobenzene (Scheme 1, bottom).
Scheme 1. Introduction of the 5-CD$_3$ group to SD-560 by functional group interconversion

In 2008, Siege and Baldrige reported the synthesis of a deuterated pentaarylcorannulene via Pd-mediated Negishi cross-coupling of syn-pentachlorocorannulene with 2,6-di(methyl-d$_3$) anisylzinc chloride (Scheme 2). The CD$_3$ group in the Negishi reagent was synthesized in a two-step procedure from the corresponding methyl ester via LiAlD$_4$-mediated reduction followed by mesylation, and LiAlD$_4$-mediated OMs-D exchange.

Scheme 2. Synthesis of deuterated pentaarylcorannulene

Apart from reducing the corresponding aryl ester, anhydride, or nitrile functional groups, the C-trideuteromethylation could also be accomplished via the reduction of the double bond. In 2014, Pizzano and co-workers reported the highly enantioselective synthesis of CDH$_2$-, CD$_2$H-, or CD$_3$-labeled 2-octyl benzoates through asymmetric hydrogenation/deuteration of 1-hexylvinyl benzoate or 2,2-dideutero-1-hexylvinyl benzoate using an Rh(I) catalyst surrounded by a chiral phosphine-phosphite hybrid ligand (Scheme 3). The nondeuterated and deuterated vinyl benzoates were prepared by Ru-catalyzed addition of benzoic acid to (deuterated) oct-1-yne in the presence of H$_2$O or D$_2$O, respectively. The hydrogenation of those deuterated vinyl benzoates was carried out using a chiral Rh(I) complex with D$_2$ gas to afford the CD$_3$-labeled 2-octyl benzoates.
Scheme 3. Enantioselective synthesis of CDH$_2$-, CD$_2$H$_x$-, or CD$_3$-labeled 2-octyl benzoates via asymmetric hydrogenation/deuteration

In 2015, Yoshimatsu and co-workers completed the synthesis of trideuteromethylated pyrroles and furans via metal-free deuterative cyclization of N- or O-tethered sulfanyl 1,6-diynes in the presence of NaBD$_4$/EtOD (Scheme 4). The deuteration regioselectively occurs at the methylene and methyl groups of heterocycles with high deuteration incorporation. The authors proposed a mechanism involving an initial DBU-mediated H-D exchange of the terminal alkyne with EtOD affording the deuterated diyne B, which could undergo two-fold base-induced alkyne-allene isomerization-deuteration to give the bis(allene) intermediate D. The intramolecular cyclization of D followed by a nucleophilic addition of deuteride on the resulting cationic intermediate E affords the final trideuteromethylated heterocycles.

Scheme 4. Synthesis of trideuteromethylated pyrroles and furans via cyclization of N- or O-tethered sulfanyl 1,6-diynes

In 2018, Wang and co-workers achieved the selective $\alpha$-monomethylation of arylacetonitriles and arylacetamides using R$_3$N-BH$_3$/DMF system as an in-situ methyl source (Scheme 5). Mechanistic studies suggest that the carbon and one hydrogen atom of the methyl group arise from the formyl group of DMF and the other two hydrogen atoms originate from R$_3$N-BH$_3$. By
tuning the corresponding deuterium sources, the reaction system enables selective incorporation of CDH$_2$, CD$_2$H, and CD$_3$ moieties using Me$_2$NH-BH$_3$/d$_7$-DMF, Me$_3$N-BD$_3$/DMF, and Me$_3$N-BD$_3$/d$_7$-DMF systems, respectively. They showed the synthetic utility of the methylation method with the synthesis of anti-inflammatory flurbiprofen and its deuterium-labeled derivatives. The α-trideuteromethylation is initiated by the deprotonation of the very acidic benzyllic C(sp$^3$)–H bond. Nucleophilic attack of the resulting carbon anion A to d$_7$-DMF affords the hemiaminal B, which undergoes deuteride reduction after dehydration to give the deuterated α-dimethylaminomethyl intermediate D. After an E1cB elimination of (CD$_3$)$_2$NH from the intermediate D, the resulting acrylonitrile E undergoes further deuteride reduction to afford the final C-CD$_3$ product.

Scheme 5. Synthesis of flurbiprofen and its D-containing analogs and the proposed reaction mechanism

1.2. H-D Exchange of Acidic Methyl Groups

As a time- and cost-saving alternative to those mentioned above, the direct H-D exchange enables the direct and late-stage deuterium labeling of the targeted organic molecules. Acid/base-dependent H/D exchange is among the oldest methods for the deuteration of a methyl group. Various base/deuterium source combinations such as NaOD/D$_2$O, Na$_2$CO$_3$/D$_2$O, NaOH/MeOD, KOBu/DMSO-d$_6$, and KOH/DMSO-d$_6$ have been employed in the deuteration of (hetero)aryl, allyl and acetophenone methyl groups (Scheme 6).
Scheme 6. Selected examples of base-promoted H-D exchanges

Matsubara and co-workers demonstrated that molecular sieve could also serve as a weak solid base in \( \alpha \)-deuteration of Wittig salts and acetophenone with D\(_2\)O (Scheme 7).\(^{29}\)

\[
\begin{align*}
\text{Scheme 7. Molecular sieve-catalyzed hydrothermal H-D exchange of Wittig salts and acetophenone} \\
\text{Compared with base-catalyzed H-D exchanges, the examples of acid-catalyzed H-D exchange are fewer. In 2005, Evchenko and co-workers reported trifluoroacetic anhydride (TFAA)-catalyzed H-D exchange of acetylferrocenes using D\(_2\)O as the deuterium source (Scheme 8).}\(^{30}\) The deuterium incorporation selectively occurred at the acetyl group without the interference of the cyclopentadienyl ring protons. \\
\text{Scheme 8. TFAA-catalyzed H-D exchange of acetylferrocenes} \\
\end{align*}
\]

In 2017, Yin and co-workers reported benzoic acid-catalyzed regioselective deuteration of the methyl groups of \( N \)-heteroarylmethanes using D\(_2\)O as the deuterium source (Scheme 9).\(^{31}\) The deuteration was observed at the 2- or 4-methyl groups of \( N \)-heteroarylmethanes, whereas no
deuteration occurred at the 3-methyl group. For substrates containing both 2- and 4-methyl groups, the deuteration at the 4-methyl group seems to be faster. Mechanistically, the methyl or methylene groups are activated by the Brønsted acid through an enamine intermediate. As illustrated in Scheme 9, protonation at the heteroarene nitrogen affords a cation intermediate. After either direct deprotonation at the C-2 methyl group or resonance/deprotonation at the C-4 methyl group—the corresponding enamine intermediate is formed. Final deuteration at the exo-methylene group of the enamine intermediate with D$_2$O delivers the deuteriomethylated heteroarenes.

Scheme 9. Brønsted acid-catalyzed deuteration at methyl groups of N-heteroarylmethanes and proposed mechanism

In 2017, Thompson and co-workers reported the synthesis of trideuteromethylated dipyrrins via microwave-promoted deuterium exchanges at the 1-methyl group of dipyrrins using CD$_3$OD or mixed CD$_3$OD/CDCl$_3$ as the deuterium source without using either acid nor base.$^{32}$ The deuteration of 1-methyl substituted dipyrrin is achieved due to the involvement of an exo-cyclic alkenyl tautomer C, which is in equilibrium with another two tautomers A and B (Scheme 10.a). For the 1,9-dimethyl substituted dipyrrins 2 and 3, the corresponding D$_7$-products resulting from H-D exchanges at both methyl groups and N-H were obtained (Scheme 10.b, entries 2 and 3). It was found that N-methyl 1-methyl dipyrrin 4 failed to participate in the deuteration since the critical dipyrrin exo-cyclic alkenyl tautomer C required for the deuteration could not be formed (Scheme 10.b, entry 4). Furthermore, the deuteration of electron-withdrawing group-containing asymmetric dipyrrins regioselectively occurred at the α-methyl group distal from the electron-withdrawing group (Scheme 10.c).
Transition metal are prone to catalyze H-D exchanges without the need for an additional external acid or base. Generally, the selectivity of heterogenous H-D exchange is poor, and it is suitable for the introduction of multiple deuterium atoms in a single step. For instance, in 2008, Sajiki and co-workers reported deuteration of methyl-substituted aromatics with D$_2$O using a mixture of Pd/C and Pt/C as the synergistic catalyst (Scheme 11).$^{33}$ The H-D exchange of anilines occurred efficiently at the C(sp$^3$)–H benzylic bonds, along with the less acidic C(sp$^2$)–H bond affording fully deuterated aromatic derivatives.

Scheme 11. Multiple deuterations of arenes using the Pd/C-Pt/C-D$_2$O-H$_2$

In 2009, Derdau and co-workers reported the use of a NaBD$_4$-activated Pd/C and Pt/C catalyst mixtures in highly efficient global deuteration of 8-methylquinoline and mefenamic acid using D$_2$O as the deuterium source (Scheme 12.a).$^{34}$ The multiple deuterated products could serve as internal standards for LC-MS/MS investigations. In the same year, the NaBH$_4$-activated Pt/Pd/C catalytic system was utilized by Sajiki and co-workers in multiple deuterations of 1,2,4,5-tetramethylbenzene in D$_2$O (Scheme 12.b).$^{35}$ Besides the methyl groups, the highly hindered C3 and C6-aromatic hydrogens were also efficiently deuterated.
In 2009, selective vinyl and allylic C–H bond labeling of various alkenes were achieved by Grotjahn and co-workers via a bifunctional Ru-catalyzed H-D exchange and olefin isomerization using inexpensive D₂O as the deuterium source (Scheme 13).³⁶ A series of alkenes with a terminal CD₃ group were synthesized. An alkene zipper Ru-catalyst was used. The N-heterocyclic ligand (NHC) also served as an internal base to facilitate the H-D exchange and isomerization. It should be noted that the deuteration of 4-allyl-anisoles, diallyl ethers, and 4-methyl-1-pentene regioselectively occurred at the C1 and C3-positions, leaving the C2 proton intact.

Scheme 13. Ru-catalyzed H-D exchange and olefin isomerization with D₂O

Organocatalysts could also promote the H-D exchange. In 2020, Chi and co-workers disclosed an early example of NHC carbene-catalyzed H-D exchanges of enals at allylic C(sp³) and C(sp²) sites using D₂O as the deuterium source (Scheme 14).³⁷ With an aminoidanol-derived NHC as precatalyst, DABCO as base and phenazine as oxidant, a diversity of β-methyl containing β-aryl or β-alkyl enals were deuterated to afford a series of α-D-β-CD₃ substituted 2-alkenoic acids/esters with good yields and high deuterium incorporation. The reaction is scalable, and the products could further be transformed into a range of deuterated allylic derivatives, aliphatic derivatives, and polydeuterated drugs via manipulations of the carbonyl and allylic functionalities. In terms of mechanism, a nucleophilic attack of the NHC to the enal’s aldehyde group generates the intermediate A. The Breslow intermediate B is formed after a hydrogen transfer and it is oxidized to give the α,β-unsaturated triazolium ester intermediate C. Base-promoted γ-carbon deprotonation and reversible enolization affords a vinyl dienolate intermediate D, which is deuterated (E) through iterative base-promoted γ-carbon deprotonation and reversible enolization followed by final hydrolysis to afford the corresponding 2-alkenoic acids and regenerate the carbene catalyst.

Scheme 14. NHC carbene-catalyzed H-D exchange with D₂O
1.3. Halogen/Metal Exchange

The aromatic metalation is a valuable protocol for the construction of well-decorated (hetero)arenes. Aromatic lithiation is carried out by lithium–hydrogen or lithium–halogen exchange. Once generated, the aryllithiums react with external electrophiles, CD$_3$I in this case, to afford the C-CD$_3$ functionalized (hetero)arenes. Since organolithium reagents are highly nucleophilic, additional protection and deprotection sequences are required for compounds bearing sensitive groups (Scheme 15.a).\textsuperscript{38} The synthesis of SD-560 through lithium–halide exchange strategy demonstrated its synthetic utility.\textsuperscript{14} As shown in Scheme 15.b, metalation of the bromopyridine with $n$-BuLi followed by trideuteromethylation with CD$_3$I successfully introduces the CD$_3$ group. Interestingly, the halogen-CD$_3$ exchange was also directly carried out from CD$_3$Li rather than the mixture of $n$-BuLi and iodomethane-d$_3$. The aryl lithium formed could be trapped by the in-situ generated CD$_3$I to afford the trideuteromethylated arene. For example, in 2015, CD$_3$Li-mediated iodine-methyl exchange of a 3-iodofuran compound was reported by Knight and co-workers as a key step in the total synthesis of a trideuteromethylated furan fatty acid (Scheme 15.c).\textsuperscript{39}
Scheme 15. C(sp²)-trideuteromethylation via lithium/halide exchange

1.4. Trideuteromethylation using Trideuteromethylation Agent Surrogates

The most traditional methods for α-trideuteromethylation of carbonyl compounds rely on base-promoted α-deprotonation followed by nucleophilic trapping of the resulting enolate with deuterated methyl electrophiles such as CD₃I. As example, in 2008, Covey and co-workers reported the synthesis of the C19-trideuteromethyl analog of the neuroactive steroid ent-testosterone using CD₃I for the introduction of the C-19 angular methyl group after a Li/NH₃ mediated reduction of the double bond (Scheme 16). Subsequent ketal deprotection and adol reaction gave ent-testosterone-19,19,19-d₃, which was then converted into the GABA_A receptor potentiators ent-androsterone-19,19,19-d₃ and ent-etiocholanolone-19,19,19-d₃ using established literature procedures.

However, CD₃I is a highly toxic reagent (carcinogenic), and it is expensive. Therefore, researchers have focused on finding surrogates of electrophilic trideuteromethyl sources. Most of the strategies involve deuterated solvents' derivatization (e.g., d₆-DMSO, CD₃OD) by either premodification or in-situ hydrogen borrowing.

In 2019, Chen and Wang developed a new trideuteromethylation reagent trideuteromethyl sulfoxonium iodide (TDMSOI) for "one-pot" C-trideuteromethylation of active methylene


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12
compounds (Scheme 17). As a safer alternative to the commonly used CD$_3$I and (CD$_3$)$_2$SO$_4$, TDMSOI is produced by sulfoxonium metathesis between trimethyl sulfoxonium iodide (TMSOI) and d$_6$-DMSO. After its preparation, TDMSOI is directly engaged in subsequent trideuteromethylation in a "one-pot" manner. To overcome the intrinsic reversibility of the metathesis process, a large excess of d$_6$-DMSO had to be used. Mechanistically, the sulfoxonium metathesis begins with heat-mediated decomposition of TMSOI to give DMSO and CH$_3$I. CH$_3$I reacts with d$_6$-DMSO to form a mixed sulfoxonium, which undergoes a second decomposition to give CD$_3$SOCH$_3$ and CD$_3$I. The final combination of CD$_3$I with d$_6$-DMSO affords TDMSOI, which reacts with active methylene compounds to provide either the mono- or double C-trideuteromethylated products.

Scheme 17. C-trideuteromethylation of acidic C–H bond with TDMSOI

In 2015, Cai and co-workers reported the use of CD$_3$OD in [Cp*IrCl]$_2$-catalyzed C3-trideuteromethylation of indole with the in-situ formation of trideuteromethylation source surrogate through hydrogen borrowing strategy (Scheme 18). The reaction was performed under air atmosphere, and the corresponding d$_3$-skatole was successfully synthesized in 84% yield with 98% deuterium incorporation. The interaction between the catalyst and CD$_3$OD affords deuterated formaldehyde and a metal deuteride. A Friedel-Craft-like reaction between indole and deuterated formaldehyde gives the C3-alkylated indole, and its dehydration leads to the formation of a 3-(methylene-d$_2$)-3H-indole intermediate, which is reduced by the metal deuteride to give the final C3-trideuteromethylated indole.

Scheme 18. [Cp*IrCl]$_2$-catalyzed C3-trideuteromethylation of indole with CD$_3$OD and proposed mechanism
Morrill and co-workers reported a similar procedure for the preparation of \(d_3\)-skatole, albeit they employed Knölker-type (cyclopentadienone)iron carbonyl complex. As outlined in Scheme 19, the reaction begins with Me\(_3\)NO-mediated CO decoordination of the iron carbonyl complex to form the active iron complex, which abstracts deuteride from \(d_4\)-methanol to afford an iron-deuteride species and \(d_2\)-formaldehyde. After several similar steps—that are described above—the final trideuteromethylated product is obtained.

Scheme 19. Fe-catalyzed C3-trideuteromethylation of indole with CD\(_3\)OD and proposed mechanism

Knölker-type Fe complex also catalyzes the trideuteromethylation of propiophenone with CD\(_3\)OD to afford the \(\alpha\)-D, \(\alpha\)-CD\(_3\)-substituted ketone derivative in more than 95% yield with a high level of D-incorporation (Scheme 20). Mechanistically, a hydrogen borrowing process between the active iron complex and \(d_4\)-methanol generates an iron-deuteride species and \(d_2\)-formaldehyde. Aldol reaction of the latter with ketone gives an enone intermediate which undergoes deuteration to provide the \(\alpha\)-(D, CD\(_3\))-substituted product together with the catalytically active Fe species.

Scheme 20. Fe-catalyzed \(\alpha\)-deuteration-\(\alpha\)-trideuteromethylation of ketone with CD\(_3\)OD

In 2019, Sortais and co-workers reported the first Mn-catalyzed \(\alpha\)-methylation of ketones and esters with methanol \textit{via} hydrogen borrowing strategy using a manganese catalyst possessing a 2,6-diaminopyridine backbone (Scheme 21). By replacing MeOH with CD\(_3\)OD, \(\alpha\)-deuterated-\(\alpha\)-trideuteromethylated ketone and trideuteromethyl ester products were obtained from the corresponding dihydrochalcone and methyl 2-(naphthalen-2-yl)acetate substrate, respectively. The low yield of the \(\alpha\)-trideuteromethylated ester is due to the difficulty with isolation.
The same year, Rueping and co-workers reported Mn-catalyzed α-deuteration-α-trideuteromethylation of ketones with $\text{CD}_3\text{OD}$ using air- and moisture-stable aromatic and cationic diphenylphosphine-based Mn-complex, with water being produced as the sole by-product (Scheme 22). A range of ketones, including propiophenones and cyclic, heteroaromatic, and aliphatic ketones, was trideuteromethylated. When $\text{CD}_3\text{OH}$ was used instead of $\text{CD}_3\text{OD}$, the corresponding α-trideuteromethylated ketone was obtained. For substrates containing benzylic positions, H-D exchange was also observed. Furthermore, double trideuteromethylation occurred when acetophenone derivatives were used as substrates.

In 2019, Renaud and co-workers achieved the synthesis of α-methylated α-alkylated ketones through Fe-catalyzed tandem three-component dialkylation of methyl ketones with benzyl...
alcohols and methanol (Scheme 23).\(^{50}\) The reaction is established on the hydrogen borrowing strategy and uses a well-defined cyclopentadienone Fe-carbonyl complex. Due to the more facile dehydrogenation of benzyl alcohol than methanol, the reaction proceeds via a chalcone intermediate instead of a phenylpropenone intermediate. This mechanistic hypothesis had been verified by the reaction between dihydrochacone and CD\(_3\)OD, which has led to a CD\(_3\)-labeled ketone with full deuterium incorporation at the $\alpha$-carbonyl position.

Scheme 23. Tandem three-component alkylation of ketones and mechanistic study

1.5. Transition Metal-Catalyzed Cross-Coupling Reaction

Transition-metal-catalyzed cross-coupling reactions have emerged over recent decades as favored route for swift construction of C(sp\(^2\))–C(sp\(^2\)) or even C(sp\(^2\))–C(sp\(^3\)) bonds in both chemical industry and academia.\(^{51}\) Such methodologies have become the choice of carbon–carbon bond forming methodology over more conventional approaches based on organometallic reagents due to milder reaction conditions, broad functional group tolerance, and use of less toxic reagents. The formation of C(sp\(^2\))–CD\(_3\) bonds is not exempt from the implementation of catalysis in organic synthesis. There are two cross-coupling possibilities between (1) aryl (pseudo)halides and trideuteromethyl organometallic reagents [CD\(_3\)M] or (2) (hetero)aryl–metal and electrophilic trideuteromethyl reagents.

Several CD\(_3\) organometallic reagents, like CD\(_3\)MgI, CD\(_3\)Li, CD\(_3\)B(OH)\(_2\), and CD\(_3\)-BF\(_3\)K, have been successfully utilized in such cross-couplings. In 2011, CD\(_3\)MgI was used by Huang and co-workers in Ni(PPh\(_3\))\(_2\)Cl\(_2\)-catalyzed synthesis of 2-(methyl-$d_3$)quinoline by cross-coupling with 2-bromoquinoline (Scheme 24a).\(^{52}\) In 2017, Feringa and co-workers reported the in-situ formation of CD\(_3\)Li from CD\(_3\)I and 'BuLi and directly used it in an ultrafast (2 min), oxygen-activated, Pd-nanoparticle-catalyzed cross-coupling with 2-bromonaphthalene (Scheme 24.b).\(^{53}\) In the same year, CD\(_3\)B(OH)\(_2\) and CD\(_3\)-BF\(_3\)K were used by Falb and co-workers in Pd-catalyzed Suzuki-Miyaura methylation with 5-bromo-1-phenylpyridin-2(1H)-one (Scheme 24.c).\(^{14}\) The cross-coupling serves as the final step in a highly efficient and green synthetic route of SD-560. It should be noted that CD\(_3\)B(OH)\(_2\) used in this study is commercially available, and CD\(_3\)-BF\(_3\)K had been prepared with inexpensive KHF\(_2\).
Scheme 24. Transition metal-catalyzed cross-coupling of (hetero)aryl halides with CD₃ organometallic reagents

Most of these deuterated methylmetallic reagents are either unavailable or available at a prohibitively expensive cost. To overcome such limitations, in 2016, Liao and co-workers reported the synthesis of trideuteromethylated arenes via Ni-catalyzed reductive cross-coupling of (hetero)aryl halides with CD₃I (Scheme 25). The reaction displayed a broad substrate scope, and various heteroaryl groups and vinyl groups are tolerated. By doubling the amounts of reagents, the reaction is also amenable to double trideuteromethylation. This method’s synthetic utility is further demonstrated in gram-scale two-step synthesis of SD-560 from 5-bromopyridin-2-ol in 70% overall yield. The authors proposed a Ni⁰/NiII catalytic cycle where transmetallation between ArNiIIX and CD₃ZnI₂(Na⁺)² is involved.

Scheme 25. Ni-catalyzed reductive cross-coupling of (hetero)aryl halides with CD₃I and the proposed mechanism

In 2018, Komeyama and co-workers disclosed the use of CD₃OTs in Ni/Co(salen)-catalyzed reductive cross-coupling with (hetero)aryl halides (Scheme 26). Iodide additives such as KI (for aryl iodide) and Et₄NI (for aryl chloride, bromide, and tosylate) are needful. The authors suggested that the addition of iodide salts promote the generation of CD₃I from CD₃OTs or
promote the Mn-mediated catalyst reduction. Their mechanism involves Mn-mediated reduction of Ni(II) and Co(II) catalysts to give two active catalysts: [Ni(0)] and [Co(I)] D. Then, oxidative addition of aryl halides to [Ni(0)] followed by Mn-mediated reduction of the resulting Ar-Ni(II)-X species A gives the Ar-Ni(I) intermediate B. Meanwhile, the reaction of CD$_3$OTs with the nucleophilic [Co(I)] catalyst D affords the CD$_3$-[Co(III)] intermediate E. A single electron transfer-mediated transmethylation between B and E gives the high-valent Ar-[Ni(III)X]-CD$_3$ intermediate C along with regeneration of the catalytically active [Co(I)] species. Upon reductive elimination, the intermediate C releases the CD$_3$-arene product and [Ni(I)]-X species; the latter undergoes Mn-mediated reduction to regenerate the [Ni(0)] catalyst.

Scheme 26. Ni/Co(salen)-catalyzed reductive cross-coupling of (hetero)aryl halides with CD$_3$OTs

In 2018, Hartwig and co-workers reported the use of PO(OCD$_3$)$_3$ for the trideuteromethylation of (hetero)aryl pinacolboronic esters using CuI and LiI as a dual catalytic system and LiO'Bu as the activator (Scheme 27).$^{58}$ By combining this methodology with Ir-catalyzed C–H borylation, the authors disclosed the formal “late-stage C–H bond” trideuteromethylation of guaiazulene (Scheme 27b). PO(OCD$_3$)$_3$ serves as an indirect CD$_3$ source in this reaction. In fact, the actual methylating agent is CD$_3$I, which is slowly released from iodide and PO(OCD$_3$)$_3$. The reaction of CuI with LiO'Bu affords BuO-Cu species, which undergoes transmetalation with ArBpin to give aryleopper species. Meanwhile, ArBpin also reacts with LiO'Bu to form the Li[ArBpin(O'Bu)] boronate complex. The sequestered O'Bu in this complex becomes less nucleophilic and thus unreactive toward CD$_3$I. Furthermore, the loosely bound Li$^+$ in the complex serves as a Lewis acid to catalyze the slow formation of CD$_3$I from PO(OCD$_3$)$_3$ and iodide. Finally, the slowly released CD$_3$I rapidly reacts with the aryllcopper intermediate to afford the desired trideuteromethylated product.
In 2015, Maiti and co-workers developed a Pd-catalyzed synthesis of 2,3-disubstituted benzofuran derivatives via oxidative annulations between phenols and alkenylcarboxylic acids (Scheme 28). From aliphatic α,β-unsaturated carboxylic acids, 3-methylene-2,3-dihydrobenzofurans, or 3-methyl-2,3-disubstituted benzofurans were synthesized depending on the electronic nature of the phenol substituents. In general, electron-withdrawing groups on the phenol favor the former's formation, while electron-donating groups favor the latter. On the other hand, 3-ethylidenedihydrobenzofurans were synthesized from conjugated 5-phenylpent-2,4-dienoic acid. Interestingly, with the addition of D$_2$O, an array of 3-(methylene-d$_2$)-2,3-dihydrobenzofurans, 3-CD$_3$-2,3-disubstituted benzofurans, and 3-(methylene-d$_2$)-2,3-dihydrobenzofurans could be synthesized via deuterium-exchange. The reaction starts with an ortho-palladation of phenols affording a palladium-phenolic complex. The insertion of the α,β-unsaturated carboxylic acids into the C-Pd bond of the palladium-phenolic complex and decarboxylation affords the Pd-allyl species A, which undergo deuterium incorporation, cyclization, and β-hydride elimination to give 3-(methylene-d$_2$)-2,3-dihydrobenzofurans and 3-CD$_3$-2,3-disubstituted benzofurans.
In 2018, Liao and co-workers reported enantioselective Cu-catalyzed trideuteromethylboration of styrenes and unactivated aliphatic olefins using CD$_3$I in the presence of bis(pinacolato)diboron (B$_2$Pin$_2$) (Scheme 29). The trideuteromethylboronated products are easily oxidized into the corresponding alcohols. This reaction requires the use of SOP for styrenes, β-substituted styrenes, while trideuteromethylboration aliphatic olefins were carried out using (R,R)-quinoxP*. The reaction of β-substituted styrenes is very stereoselective, affording exclusively syn-addition products. Furthermore, anti-Markovnikov products were obtained for the aliphatic olefins. The authors proposed that the reaction proceeds through Cu-B addition across the C–C double bond followed by cross-coupling of the resulting alkylecuprate with CD$_3$I.

1.6. Transition-Metal-Catalyzed C–H Bond Trideuteromethylation
In the past two decades, transition metal-catalyzed C–H bond functionalization has become a suitable atom- and step-economical alternative to cross-coupling reactions owing to prefunctionalization is not required and they did not generated metals salts as waste. 61-64 When these reactions are performed with trideuteromethyl percussors, they become elegant methods for forming C(sp²)–CD₃ and C(sp³)–CD₃ bonds. Despite its high toxicity, CD₃I is the most frequently used trideuteromethyl reagent in C–H bond trideuteromethylation.

In 2014, Yu and co-workers reported an early example of C(sp²)–H bond trideuteromethylation using CD₃I (Scheme 30.a). 65 The reaction occurred through the vinylic C(sp²)–H bond cleavage with the help of a weakly directing amide group using 10 mol% Pd(TFA)₂ associated with 9-methylacridine as the ligand. In 2015, Chen and co-workers disclosed an isolated example of Pd-catalyzed 8-aminoquinoline (AQ)-directed C(sp²)–H trideuteromethylation of an ortho-methyl substituted benzamide with CD₃I using NaHCO₃ and (BnO)₂PO₂H (Scheme 30.b). 66 Pd-catalyzed C–H bond trideuteromethylation is not limited only to C(sp²)–H bond; the (sp³)–H trideuteromethylation of 8-aminoquinoline-coupled phthaloyl alanine occurred in the presence of 10 mol% of Pd(OAc)₂ and TFA at room temperature in 89% yield (Scheme 30.c). 67

![Scheme 30. Pd-catalyzed C(sp²)–H trideuteromethylation with CD₃I](image)

In 2018, CD₃OTs was employed by Yoshikai and co-workers in cobalt-catalyzed directed ortho-trideuteromethylation of arenes (Scheme 31). 68 A catalytic system comprised of Co(acac)₃, N,N'-di(2-butyl) benzimidazolium bromide, and neopentyl Grignard reagent promoted the trideuteromethylation directed by N-aryl imine and 2-pyridyl groups. The actual trideuteromethylating agent in the present reaction seems to be CD₃Br, which is in-situ generated from CD₃OTs and the Grignard reagent. Mechanistically, cyclometallation of the imine with a low-valent R-[Co] species A generated from the cobalt precatalyst, and the Grignard reagent gives the cobaltacyle species B. SET from the cobalt center to the in-situ formed CD₃Br generates a pair of oxidized cobaltacyle and CD₃ radical (C), which undergo radical rebound to give the intermediate D. Reductive elimination of D gives the trideuteromethylated arene product together with [Co]Br, the transmetalation of the latter with the Grignard reagent regenerates the low-valent cobalt species A.
Soon after, CD$_3$OTs was used by Zhou and co-workers in Catellani-type dual-tasked C–H trideuteromethylation of aryl iodides (Scheme 32)$.^69, 70)$ Diverse ortho-trideuteromethylated derivatives were synthesized by terminating the reaction with Heck, Suzuki, or hydrogenation reaction. The applicability of the dual-tasked trideuteromethylation was also demonstrated on late-stage modification of a biologically important phenylalanine derivative and the derivative of the antiatherosclerotic drug ezetimibe. When aryl iodides without ortho-substituents are used in the presence of a double amount of CD$_3$OTs, the corresponding double trideuteromethylation products are obtained.

Inspired by radical transferase S-adenosylmethionine (SAM) and the design principle of Umemoto’s reagent, Shi and co-workers developed a biomimetic methylating agent DMTT (5-(methyl-d$_3$)-5H-dibenzo[b,d]thiophen-5-ium trifluoromethane sulfonate) for mild and selective

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[Scheme 31. Co-catalyzed directed ortho-trideuteromethylation of arenes with CD$_3$OTs and proposed mechanism]

[Scheme 32. Pd-catalyzed Catellani-type C–H bond trideuteromethylation]
trideuteromethylation of various nucleophiles (Scheme 33).\textsuperscript{71} DMTT is easily prepared as a bench-stable solid from dibenzo[\textit{b,d}]thiophene and CD\textsubscript{3}OD. This reagent is utilized in Pd-catalyzed pyridine- or acetylamino-directed \textit{ortho}-C\textsubscript{(sp\textsuperscript{2})}-H \textit{mono}- or \textit{di}-methylation of several organic and drug molecules.

Scheme 33. Pd-catalyzed C–H trideuteromethylation with DMTT

In 2019, Shi and co-workers reported the use of \textit{d}\textsubscript{6}-Ac\textsubscript{2}O in Rh-catalyzed, indole \textit{N}-\textit{P}Bu\textsubscript{2}-directed C7-selective C–H trideuteromethylation of indoles (Scheme 34).\textsuperscript{72} A variety of indoles readily underwent selective C7-trideuteromethylation to afford the desired products in high yields and deuterium ratios, with partial deuterium incorporation at the acidic C-3 position. C-3 substituted indoles. \textit{N}-\textit{P}Bu\textsubscript{2} protected carbazoles were also suitable partners for this reaction. For the indole bearing a C-3 acetyl group, partial H-D exchange occurred at the $\alpha$-acidic hydrogen. Furthermore, double trideuteromethylation of (bis)indole substrate was also carried out in good yield. The P(III) directing group is removable by treatment with TBAF to afford a free indole. Mechanistically, coordination of Rh\textsuperscript{1-X} A with the directing group affords the intermediate B, which undergoes dehydrohalogenation via the intermediate C to give the rhodacycle D. Oxidative addition of \textit{d}\textsubscript{6}-Ac\textsubscript{2}O onto the rhodacycle affords the Rh\textsuperscript{III} intermediate E, which after decarbonylation and reductive elimination produces the final trideuteromethylated product and regenerates the catalytically active species A.

Scheme 34. Rh-catalyzed C7-trideuteromethylation of indoles with \textit{d}\textsubscript{6}-Ac\textsubscript{2}O and proposed mechanism
In 2012, Deng and co-workers reported the early use of $d_6$-DMSO in Pd-catalyzed, N–O directed C–H bond trideuteromethylation of 3-phenylisoquinoline $N$-oxide in the presence of $(n$-Bu)$_4$NOAc/ZnO/Bu$_3$N/air (Scheme 35). The trideuteromethylation occurred together with N–O cleavage to afford 1-(methyl-$d_3$)-3-phenylisoquinoline in 60% yield. $(n$-Bu)$_4$NOAc serves as the phase-transfer catalyst and acts as a base to reduce the N–O bond. Meanwhile, the combination of ZnO/Bu$_3$N also serves as a base to improve the N–O bond's cleavage. In terms of the reaction mechanism, the coordination of [PdL$_n$] with the isoquinoline $N$-oxygen followed by C–H oxidation-carbopalladation-complexation of the resulting intermediate A affords the intermediate B, which undergoes C–S oxidative cleavage of $d_6$-DMSO and CD$_3$ insertion to give the intermediate C and CD$_3$S(O)O$^–$. Reductive elimination of the intermediate C and [PdL$_n$]/PTC/bases-mediated N–O reduction of the resulting trideuteromethylated isoquinoline $N$-oxide gives the final 1-CD$_3$-substituted isoquinoline.

Scheme 35. Pd-catalyzed C–H trideuteromethylation of isoquinoline $N$-oxide with $d_6$-DMSO and proposed mechanism

In 2021, Johansson and Martin-Martute reported the use of MeBF$_3$K and CD$_3$BF$_3$K in [Cp*IrCl$_2$]$_2$-catalyzed directed ortho C–H methylation and trideuterodmethylation of benzoic acids. The reaction is moisture and air-insensitive and occurs with exclusive regioselectivity ortho to the carboxylic group despite the presence of other possible directing groups in the same molecules. CD$_3$BF$_3$K used in this study was prepared using the procedure reported by Falb and coworkers. The trideuteromethylation occurs with comparable yields and regioselectivities to C–H bond methylation and the reactions were successfully applied in late-stage functionalizations of several structurally complex drug molecules.
In 2013, non-directed C(sp)–H trideuteromethylation of alkynes was disclosed by Li and co-workers during the mechanistic elucidation of Pd-catalyzed methylation of terminal alkynes with dimethyl sulfonium ylides (Scheme 37). An intermolecular competition experiment between dimethyl and bis(trideuteromethyl) sulfonium ylides was performed, affording methyl-functionalized internal alkynes and the deuterated product in a ratio of 1.2:1. This suggests that the methyl group comes from the ylide, and the cleavage of the S–CH₃ bond is favored over the S–CD₃ bond. Oxidative addition of S–CH₃ on Pd⁰Ln affords the intermediate B, which reacts with alkyne to in-situ lead C, which upon reductive elimination affords the methylated product and closes the catalytic cycle.

Scheme 37. Pd-catalyzed intermolecular competitive C(sp)–H methylation and trideuteromethylation of terminal alkynes and proposed mechanism
1.7. Radical Reactions

Radical-based C–H functionalization and cascade reactions are convenient methods for elaborating aromatic heterocycles. In most cases, the reaction is triggered by the generation of radicals –•CD₃ in this case– using either a stoichiometric amount of oxidants coupled with metal salts or, more recently, using a photoredox catalyst.

In 2016, Antonchick and co-workers reported an early example of Minisci-type reactions for the radical trideuteromethylation of (iso)quinolines using d₆-DMSO as a CD₃ radical source (Scheme 38). The reaction is initiated by Fe(II) salt/ hydrogen peroxide systems. The reaction exhibited a broad substrate scope tolerating both electron-donating and electron-withdrawing groups. Mechanistically, hydroxyl radical is generated by the action of iron(II) salt on H₂O₂, and adds to d₆-DMSO to be later fragmented into CD₃ radicals. A nucleophilic attack of CD₃ radical at the most electron-deficient position of the protonated aromatic ring followed by oxidation/deprotonation delivers the final trideuteromethylated (iso)quinolines.

They also extended this CD₃ radical chemistry to cascade trideuteromethylation of a set of acrylamides, including N-arylmethacrylamides, acrylamides, and N-(arylsulfonfyl)acrylamide (Scheme 39). For N-arylmethacrylamides, various nitrogen substituents, as well as α-carbonyl substituents, were tolerated. Furthermore, both α-chloroamides and α-bromoamide were obtained from acrylamides using FeCl₂ or FeBr₂ as the mediator, respectively. The reaction starts as before, but the nucleophilic attack of CD₃ radical occurred on the alkene. The generated radical undergoes cyclization/re-aromatization, oxidation/halogenation or aryl migration/desulfonylation to afford the corresponding trideuteromethylated oxindoles, α-halo-β-trideuteromethylated amides, or α-aryl-β-trideuteromethylated amide, respectively.
Qi and Li have also used $d_6$-DMSO to synthesize trideuteromethylated phenantridines and isoquinolines via CD$_3$ radical-initiated cascade trideuteromethylation/cyclization of aryl or vinyl isocyanides under Fenton conditions (Scheme 40). The authors proposed a similar generation of $^*\text{CD}_3$ promoted by Fe(II)/H$_2$O$_2$, which adds to the isocyanide and further cyclize to give the radical intermediate D. Then, Fe$^{III}$-mediated oxidation and subsequent deprotonation of D affords the trideuteromethylated products. Since deuterated methylsulfinyl acid was produced during the reaction, one equivalent of K$_2$CO$_3$ was added in some reactions to counteract the influence of the acetic acid by-product on the reaction yield.
In 2018, Qi and Li reported Fe-mediated radical azidotrideuteromethylation of acrylamides and styrenes under Fenton conditions using TMSN$_3$ and d$_6$-DMSO (Scheme 41). A series of N-aryl, N-benzyl, and N-alkylacrylamides were difunctionalized in high yields. In the case of styrenes, sometimes NH$_2$OSO$_3$H should be added to facilitate the azidotrideuteromethylation. CD$_3$ radical is firstly generated from d$_6$-DMSO with Fe(II)/H$_2$O$_2$. Once the CD$_3$ radical addition into alkenes, the carbon-centered radical A is oxidized by Fe(III). Finally, the cation B is trapped by TMSN$_3$.

In 2017, the Barriaut group and Scaiano group collaboratively developed photo-mediated (UVA) methylation of pyridines, quinolines, and phenanthridines using methanol as both the solvent and the methylating reagent in the presence of hydrochloric acid (Scheme 42). Selective formations of CD$_3$, CD$_2$H, and CDH$_2$ products could be achieved using a combination of CD$_3$OD/DCI, CD$_3$OH/HCl, or CH$_3$OD/DCI, respectively. For trideuteromethylation, the
deuterated heteroarene I is excited to its singlet state I*, which undergoes reductive quenching by CD3OD to give the deuterated radical intermediate I' and the deuterated hydroxymethyl radical. A nucleophilic attack on the deuterated heteroarene leads to the deuterated hydroxymethylated intermediate II, which is reduced by the intermediate I* to give the amino alcohol III and regeneration of the ground-state heterocycle I. The elimination of HOD from the intermediate III gives the deuterated enamine intermediate IV, which undergoes tautomerization to afford the desired trideuteromethylated product.

![Scheme 42. Photo-mediated (UVA) deuteromethylation of lepidine and proposed mechanism](image)

In 2017, similar work was developed by Li and co-workers, albeit they use CH2Cl2 as co-solvent to facilitate the generation of the hydroxymethyl radical and trifluoroacetic acid to protonate the heteroarene (Scheme 43).84 Using CD3OD as the solvent, trideuteromethylation of 2-methylquinoline was achieved in 76% yield. Deuterium-labeling experiment of 2-methylquinoline with d3-CD3OH led to 66% D-incorporation in the newly formed methyl group. This suggests that the methyl group originates from two hydrogens of the methyl group and one hydrogen of the hydroxyl group in methanol. The deuterated hydroxymethyl radical is first generated via the interaction of CD3OD with CH2Cl2 under light irradiation.

![Scheme 43. Photo-induced deuteromethylation of 2-methylquinoline with CD3OD/CD3OH and proposed mechanism](image)

In 2018, Glorius and co-workers employed d6-DMSO as CD3 radical precursor in Ir-photoredox-catalyzed C–H trideuteromethylation of heteroarenes using PhPOCl2 as the activator under visible light irradiation (Scheme 44).85 A series of quinolines and isoquinolines were successfully trideuteromethylated at C2, C4, or C1 positions depending on their substitution patterns. Furthermore, a glucose-bearing quinoline derivative was also trideuteromethylated.
The authors proposed an oxidative quenching pathway. SET from the excited Ir(III)* catalyst to the protonated heterocycle produces the heteroaryl radical B and Ir(IV). SET from B to chlorobis(trideuteromethyl)sulfonium A, which is produced from d6-DMSO and PhPOCl2, regenerates the protonated heterocycle and produces the sulfur radical. The C–S homolytic cleavage of the sulfur radical affords the CD3 radical, which undergoes nucleophilic addition onto the most electron-deficient position of the protonated heteroarene to give a radical cation. After deprotonation, the resulting trideuteromethylated heteroaryl radical C is formed and then oxidized by Ir(IV) to give the protonated trideuteromethylated product and regenerate the Ir(III) catalyst.

Scheme 44. Ir-photoredox-catalyzed trideuteromethylation of heteroarenes with d6-DMSO

In 2020, the Barriault group updated their UVA deuteromethylation of lepidine to visible-light using Ir-photoredox system (Scheme 45).86 The reaction also goes through an enamine intermediate, affording CD3, CD2H, or CDH2 adducts in comparably lower yields using the combination of CD3OD/DCl, CD3OH/HCl, or CH3OD/DCl, respectively. Mechanistically, unlike previous UV-mediated trideuteromethylation, which directly generates a deuterated hydroxymethyl radical upon reductive quench, the reaction first generates a chlorine atom, which undergoes hydrogen atom transfer (HAT) with CD3OD to give the deuterated hydroxymethyl radical.
Scheme 45. Ir-photoredox-catalyzed trideuteromethylation of lepidine with CD$_3$OD/DCI, CD$_3$OH/HCl, or CH$_3$OD/DCI and the proposed mechanism

In 2021, during their investigation on the preparation of positron emission tomography radioligands through photoredox-catalyzed tritium (CT$_3$) and carbon-11 ($^{11}$CH$_3$)–labeled methylation, MacMillan and co-workers have also reported the trideuteromethylation of Glipizide-Br (Scheme 46). The reaction involves a metallaphotoredox cross-electrophile coupling mediated by silyl radical activation of aryl halide in the presence of Ir(III) as photosensitizer and Ni(II) catalyst. They used $d_3$-methyl naphthalene-1-sulfonate as the CD$_3$ radical source.

Scheme 46. Metallaphotoredox cross-electrophile trideuteromethylation of aryl halides mediated by silyl radical activation

In 2014, Baran and co-workers described indirect methylation of heteroarenes using zinc bis(phenylsulfonyl)methanesulfinate (PSMS) as a methyl radical surrogate (Scheme 47). The
reaction proceeds via a two-step process involving TBHP-mediated (phenylsulfonyl)methylation with PSMS followed by Mg/MeOH, SmI$_2$/H$_2$O/THF, or Raney-Ni/EtOH mediated desulfonylation to reveal the methyl group. As exemplified by the three-step synthesis of trideuteromethylcafeine from cafeine, the indirect methylation protocol could be extended to trideuteromethylation via sequential dideuteration and desulfonyldeuteration of the (phenylsulfonyl)methylated intermediate by stepwise treatment with Mg/CD$_3$OD and SmI$_2$/D$_2$O. The major advantage of the two-stage process is the easy separation of the methylated product from the starting material.

Scheme 47. Radical methylation or trideuteromethylation using PSMS

1.8. Other Transformations

In 2008, Yan and co-workers prepared α-dideuteromethyl ketones and α-trideuteromethyl ketones through TiCl$_4$/Mg-promoted carbonyl-methylenation of amides with CD$_2$Cl$_2$ followed by hydrolysis of the resulting enamines with H$_2$O or D$_2$O (Scheme 48).

Scheme 48. Ti-Mg promoted synthesis of methyl and deuterated methyl ketones via coupling of amides with CH$_2$Cl$_2$/CD$_2$Cl$_2$

In 2017, Pace and co-workers achieved the synthesis of α-CD$_3$-substituted β,γ-unsaturated aldehydes from α,β-unsaturated ketones using a lithium carbenoid precursor CH$_2$Br$_2$/CD$_2$Br$_2$ and CD$_3$Li•LiI (Scheme 49). The combination of CH$_2$Br$_2$/CD$_2$Br$_2$ with CD$_3$Li•LiI firstly gives the carbenoid LiCH$_2$Br/LiCD$_2$Br together with CD$_3$I. LiCH$_2$Br/LiCD$_2$Br-mediated C1 homologation of ketone followed by Lewis acid-mediated epoxide-aldehyde isomerization and α-derivatization of the aldehyde enolate with the in-situ generated CD$_3$I leads to the desired α-CD$_3$-substituted β,γ-unsaturated aldehydes. It should be noted that deuteration at both the aldehyde and its α-position was achieved for the D$_2$-carbenoid precursor. On the other hand, only α-trideuteromethylmethylation was observed for the H$_2$-carbenoid precursor.
Scheme 49. Synthesis of α-CD₃-substituted β,γ-unsaturated aldehydes from α,β-unsaturated ketone by the use of carbenoid precursor CH₂Br₂/CD₂Br₂ and CD₃Li•LiI and proposed mechanism

In 2015, Baran and co-workers accomplished one-pot Fe-mediated hydromethylation of olefins in the presence of a mixture of PhSiH₃, CH₂O, nOctSO₂NHNH₂, and MeOH (Scheme 50). The in-situ generated formaldehyde hydrazine serves as the potential electrophilic methyl group surrogate. When they used deuterated formaldehyde or/and methanol, deuterated L-Fmoc-Leu-OMe derivatives are produced. Depending on the deuterated pattern, CDH₂, CD₂H, or CD₃ group was introduced. The authors proposed that Fe-mediated the addition of PhSiH₃ to the olefin affords the nucleophilic radical A, which undergoes C–C bond formation with the in-situ generated deuterated formaldehyde hydrazone to give the alkyl hydrazone B. Then reductive C–N bond cleavage of the alkyl hydrazone in the presence of CD₃OD produces the hydrotrideuteromethylation product.

Scheme 50. Hydromethylation/deuterated hydromethylation of unactivated olefins and proposed mechanism
2. Organic Molecules Containing N–CD₃ Bond

N-methyl amines are prevalent in a wide range of natural products, pharmaceuticals, and bioactive compounds. Several clinically meaningful N-CD₃ containing compounds have been developed (Figure 1). Their preparation mainly involves reduction methods of N-protected amines, H/D exchanges, or nucleophilic substitution of amines with electrophilic CD₃ reagents such as CD₃I and (CD₃)₂SO₄.⁹³,⁹⁴

2.1. Functional Group Conversion

As a general example of the reduction of protected amines into N–CD₃ unit, we selected the early work of Adamczyk and co-workers describing the synthesis of N-trideuteromethylated E-doxepin through the reduction of the corresponding N-doxepin carbamate using LiAlD₄ (Scheme 51).⁹⁵ This deuterated analog of doxepin is used as an internal standard for quantifying the plasma concentration of doxepin using fluorescence polarization immunoassay.

Scheme 51. LiAlD₄-mediated reduction of N-carbamate

In 2020, Rueping and co-workers succeeded the N-trideuteromethylation of amines via MgBu₂-catalyzed reduction of linear or cyclic carbamates with DBpin (Scheme 52).⁹⁶ Both N–Me carbamates and N–H carbamates were reduced into the corresponding tertiary and secondary N–CD₃ amines with quantitative D-incorporation. The authors proposed that BuMgD generated from MgBu₂ and DBPin serves as the active catalyst for the whole catalytic cycle. Deuteride addition of BuMgD to the carbamate affords the formamide A and BuMgOMe II, which reacts with DBpin to regenerate BuMgD along with MeOBpin B. A second deuteride addition of BuMgD to the formamide A affords the Mg-alkoxide intermediate III, which reacts with DBpin to regenerate BuMgD and the OBpin-hemiaminal species C. Lastly, BuMgD-mediated C–O cleavage of the species C delivers the final N-trideuteromethylated amine and BuMgOBpin IV. The reaction of IV with a third molecule of DBpin regenerates the active catalyst BuMgD and release the O(Bpin)₂ by-product D.
Besides the reduction of carbamates, the N–CD₃ group can be generated through H/D exchange using metal nanoparticles in the presence of D₂. In 2014, Rousseau and Chaudret selectively incorporated three deuterium atoms at the N-Me group of dextromethorphan using Ru nanoparticles stabilized on PVP (PVP = polyvinylpyrrolidone) (Scheme 53). The deuteration took place regioselectively at the N-Me group since other C–H bonds at the α-position of nitrogen are embedded in the six-membered ring and are thus less accessible.

In 2016, Gunanathan and co-workers reported α-selective deuteration of amines and amino acids with D₂O using monohydrido-bridged dinuclear ruthenium complex. For N-methyl substituted substrates such as N-methyl-N-benzylamine and sertraline, the deuteration selectively occurred at the N-methyl groups (Scheme 54).
2.2. *N*-Trideuteromethylation of Amines and Derivatives

Traditionally, *N*-methyl amines are prepared by reactions of primary or secondary amines with SN2-methylating agents. The *N*-methylation of primary amines is usually hampered by over methylation. Amid the previously developed TDMSOI reagent is also employed for the *N*-trideuteromethylation of phthalimide, indole, and indoline (Scheme 55). Notably, simultaneous *N*- and *O*-trideuteromethylation was observed when indoline-2-carboxylic acid was the substrate.

In 2019, Liu and co-workers reported the *in-situ* generation of CD3OTs in ipso-detosylative *N*-trideuteromethylation of *N*-tosylindoles using KOCD3 (Scheme 56). CD3OTs is generated from the nucleophilic attack of CD3O- on the sulfonamide, followed by the cleavage of the indole N–S bond. A subsequent SN2 attack of the *N* anion on CD3OTs affords the *N*-trideuteromethylation product. Alternatively, KOCD3 was also *in-situ* generated from KOtBu and CD3OD.

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Scheme 54. Ru-catalyzed α-selective labeling of amines

Scheme 55. *N*-trideuteromethylation of acidic amines with TDMSOI

Scheme 56. Detosylative *N*-trideuteromethylation of indoles with KOCD3 and reaction mechanism
As a biomimetic methylating agent, DMTT has also been used in base-promoted selective trideuteromethylation of strongly acidic sulfonamide or dicarbonyl N–H bonds in complex molecules (Scheme 57). Less acidic functional groups such as amine, amide, and hydroxyl groups remained intact under these reactions. Furthermore, using the Ni-catalyzed procedure, selective dimethylation-$d_6$ and methylation-$d_3$ were achieved for aryl/alkyl primary amines and secondary amines, respectively, without forming over-methylated quaternary ammonium salts. The Ni-catalyzed reactions exhibited a high functional group tolerance (e.g., hydroxyl, tertiary/secondary amino, and amide).

Scheme 57. $N$-trideuteromethylation of complex molecules with DMTT

In 2009, Kočovský and Malkov elucidated the mechanism of selective $N$-methylation of Boc-protected valine with MeI thanks to $N$-trideuteromethylation (Scheme 58). An isotopic labeling experiment with CD$_3$I affords the $N$–CD$_3$ product instead of the $N$–CHD$_2$ product, suggesting that the methylation proceeds via a $S_N2$ mechanism instead of an alternative mechanism involving the formation of the carbene intermediate :CD$_2$ and its insertion into the N–H bond.

Scheme 58. Mechanistic elucidation of $N$-trideuteromethylation with CD$_3$I

2.3. Reductive Amination

Besides electrophilic methylation with CD$_3$ reagents, $N$-trideuteromethylation could also be achieved via reductive amination with formaldehyde or formaldehyde equivalent in the presence of a reducing reagent such as formic acid and metal hydrides. In 2002, a microwave-assisted Eschweiler-Clarke methylation of amines was reported by Jones and co-workers using formic acid-formaldehyde mixtures as the methyl donor (Scheme 59). Since the newly introduced methyl group is derived from one carbon and two hydrogen atoms of HCHO and one hydrogen of HCOOH, selective $N$-monodeutero-, $N$-dideutero- and $N$-trideuteromethylation of trans-cinnamyl piperazine were achieved using combination of HCHO/DCOOD, DCOO/HCOOH or
DCDO/DCOOD, respectively. Furthermore, the reaction also allows for the synthesis of the antineoplastic drug Tamoxifen and its CD3 analog.

Scheme 59. Microwave-assisted methylation and deuteriomethylation of amines using the appropriately deuterated HCOOH-HCHO mixture

In 2005, Konopelski and co-workers reported the preparation of N-CD3-labeled histidine methyl ester via sequential reduction aminations with PhCHO/NaBD3CN and (CD2O)n/NaBD3CN followed by hydrogenolysis of the benzyl group (Scheme 60).102 The sequences of reductive aminations were performed in one-pot within the same flask without isolation.

Scheme 60. Reductive amination with (CD2O)n and NaBD3CN

Heck and co-workers described the combination of appropriately deuterated formaldehyde and cyanoborohydride to form stable isotope dimethyl labeling of proteolytic peptides at the α and ε-amino groups. In the presence of CD2O/NaBH3CN or 13CD2O/NaBD3CN, the corresponding N,N'-bis(dideuteromethyl) and N,N'-bis(13C-trideuteromethyl)ated products were selectively obtained, respectively (Scheme 61).103, 104

Scheme 61. Preparation of stable-isotope dimethyl labeled peptides

In 2014, Xiao and Wang achieved N-methylation of a broad range of amines using a combination of DMSO and formic acid as the methyl source (Scheme 62).105, 106 The methylation involves the transfer of a methylene group from DMSO to an amine followed by imine reduction by formic acid. Thus, selective N-monodeuteromethylation, N-dideuteromethylation, and N-trideuteromethylation were achieved using a combination of DMSO/DCO2H, d6-DMSO/HCO2H, and d6-DMSO/DCO2H, respectively. As for the trideuteromethylation, the reaction of d6-DMSO with DCOOH affords the deuterated methylthiomethylene cation intermediate C, which undergoes amine interception and CD3SH elimination to give the deuterated imine intermediate E. DCO2H-mediated reduction of the imine intermediate delivers the N-trideuteromethylated amine product.
In 2019, Beller and co-workers reported the synthesis of \( N \)-methyl-arylamines via Pd-catalyzed reductive methylation of nitroarenes with MeOH using Pd(OAc)\(_2\) associated with a sterically bulky pyridine-bearing phosphine ligand.\(^{107}\) From CD\(_3\)OH as the methyl donor three deuterated \( N \)-methyldiarylamines were synthesized with high deuteration ratio of \( N \)-methyl group (Scheme 63). Caution, the reaction is sluggish using CD\(_3\)OD. The authors explained this difference by the crucial activation of O–H bond. The Pd/ligand system plays a dual role of decomposition of methanol and reduction of the nitro group. The reaction proceeds via hydrogen-bonding of CD\(_3\)OH to the nitrogen of the pyridyl group of the ligand. O–H cleavage of CD\(_3\)OH by coordinated palladium followed by \( \beta \)-D elimination of the resulting CD\(_3\)O-Pd-H species A and subsequent reductive amination affords H-D, deuterated formaldehyde and PdL\(_n\) species. Meanwhile, Pd/L catalyzes the hydrogenation of nitroarenes to afford an aryl amine intermediate B. Condensation of B with the in-situ formed CD\(_2\)O produces a deuterated imine intermediate C which undergoes Pd-catalyzed hydrogenation to afford the final \( N \)-CD\(_3\)-arylamine.
Scheme 63. Pd-catalyzed reductive $N$-trideuteromethylation of nitroarenes with CD$_3$OH

3. Organic Molecules Containing O–CD$_3$ Bond

The ether linkage is the single most common and unifying structural feature, generally prepared by SN2 reaction between alkoxides of phenoxides with alkyl halides, so-called Williamson ether synthesis. Trideutomethyl ethers can be prepared either by forming O–CD$_3$ bond using electrophilic CD$_3$ reagents or C–OCD$_3$ bond formation via trideuteromethylation. This latter case is mostly employed for the construction of deuterated anisole derivatives. Trideuteromethyl esters are another class of molecules containing the O–CD$_3$ bond. They are generally prepared from corresponding carboxylic acids.

3.1. O-Trideuteromethylation of Phenol Derivatives and Carboxylic Acids

Classical approaches to O-trideuteromethylation generally involve nucleophilic attack of O-nucleophiles with electrophilic CD$_3$ reagents under strongly basic conditions$^{108-111}$ or acidic conditions.$^{112}$ Due to the toxicity associated with the commonly used electrophilic CD$_3$ reagents such as CD$_3$I, (CD$_3$)$_2$SO$_4$, and deuterated diazomethane, there is a strong need for the development of novel O-trideuteromethylation methods employing less toxic trideuteromethylating reagents. As described earlier, TDMSOI has been successfully utilized in "one-pot" trideuteromethylation of various nucleophiles such as active methylene compounds and amines.$^{45}$ This reagent is also useful in O-trideuteromethylation of phenols (Scheme 64.a) and carboxylic acids (Scheme 64.b). Various (hetero)aryl phenols, polyphenols, and phenol precursors of bioactive drugs smoothly participated in the reaction to afford a diversity of mono-
, double and triple \(O\)-trideuteromethylation products in good yields with high levels of deuterium incorporation. Furthermore, a series of trideuteromethyl esters were prepared from the corresponding (hetero)aryl, alkyl carboxylic acids, and cinnamic acid. Significantly, the reaction also allows simultaneous \(O\)-trideuteromethylation of a molecule containing both hydroxyl and carboxylic groups.

Scheme 64. \(O\)-trideuteromethylation of phenols and carboxylic acids with TDMSOI

In the previous section, we have discussed KOCD\(_3\) as the CD\(_3\) source for detosylative \(N\)-trideuteromethylation of \(N\)-tosylindoles (Scheme 56).\(^99\) This reaction system is also suitable for the \(ipso\)-detosylative \(O\)-trideuteromethylation of \(O\)-tosylphenols using either commercially available or in-situ generated KOCD\(_3\) as the trideuteromethylating reagent (Scheme 65).\(^99\)

Scheme 65. Detosylative \(O\)-trideuteromethylation of \(O\)-tosylphenols

In 2018, Ray and co-workers developed a novel, cheap and industrially scalable process for the synthesis of tetrabenazine and deutetrabenazine, \(i.e.,\) two drugs for the treatment of chorea associated with Huntington’s disease (Scheme 66).\(^{113}\) The methylation or trideuteromethyl group in the targets was introduced \(via\) methylation or (trideutero)methylation of the phenol intermediate with MeOH or CD\(_3\)OD using the classical Mitsunobu reaction in the presence of Ph\(_3\)P and DIAD. Unlike previous reported methods using genotoxic CH\(_3\)I and CD\(_3\)I, the novel process for the synthesis of tetrabenazine and deutetrabenazine is relatively safe.
Scheme 66. Synthesis of tetrabenazine and deutetrabenazine via Mitsunobu reaction with CH$_3$OH or CD$_3$OD

In 2019, Bissember and Coote reported an electrochemical electrophilic O-trideuteromethylation of 4-nitrobenzoic acid using air- and bench-stable TEMPO-CD$_3$ as a latent CD$_3$ source (Scheme 67). TEMPO-CD$_3$ is easily prepared from $d_6$-DMSO and TEMPO via the Fenton-type chemistry. The reaction is initiated by one-electron electrochemical oxidation of TEMPO-CD$_3$ to afford an active radical cation trideuteromethylating agent. Subsequent SN2 attack of the carboxylic anion on the radical cation leads to the formation of the desired trideuteromethyl esters along with the release of TEMPO.

Scheme 67. Electrochemical O-trideuteromethylation of carboxylic acids with TEMPO-CD$_3$

As described for N-trideuteromethylation, DMTT could also mediate selective O-trideuteromethylation of carboxylic acids and phenols in the presence of other functional groups such as alcohol hydroxyl, amino, and amide groups (Scheme 68). The reactivity of carboxylic acids is better than that of phenols. Thus, selective methylation-$d_3$ of the carboxylic group was observed when both functional groups are present in the same molecule. Furthermore, the corresponding aryl methyl ether was readily deuterated by a two-step demethylation-$d_3$-methylation process.
3.2. C(sp²)-Trideuteromethoxylation

In 2011, Jung and Bräse achieved the synthesis of monodeuterated and D₃CO-substituted arenes from resin-bound triazenes via acid-mediated triazene decomposition and deuterium-dediazoniation using CD₃OD as the deuterium source (Scheme 69). The reaction follows an ionic pathway, and the reaction outcomes of monodeuteration or trideuteromethoxylation are dependent on the electronic nature of the immobilized arenes. A two-fold deuteration of triazene resin was carried out, affording an arene with both deuterium and OCD₃ substitutions.

In 2012, Beller and co-workers reported the first several examples of Pd-catalyzed trideuteromethoxylation of (hetero)aryl halides with CD₃OD using a bulky, non-commercial adamantyl-substituted bispyrazolylphosphine as ligand (Scheme 70). The bulky ligand is used to facilitate the C–O bond formation by promoting the reductive elimination. It is worth noting that α-deuteration of the ketone occurs during the trideuteromethoxylation of 4-bromoacetophenone, which is consistent with the results reported by Hashimoto co-workers.
In the same year, Peruncheralathan and co-workers also described a similar Pd-catalyzed trideuteromethoxylation of (hetero)aryl halides with CD$_3$OD, albeit they employed $t$BuXPhos as commercially available ligand (Scheme 71). The sterically bulky diaryl phosphine ligand also reduces the competing $\beta$-hydride elimination minimizing the formation of unwanted reduced arenes. Besides mono-fold reaction, double trideuteromethoxylation efficiently occurred with 2,5-dibromo-$p$-xylene with an increased catalyst loading. Nitrogen-containing heteroaryl halides are also the trideuteromethoxylated.

In 2013, Buchwald and co-workers developed a room temperature Pd-catalyzed coupling of (hetero)aryl halides with 5 equivalents of CD$_3$OD (Scheme 72). The reactions were achieved with the assistance of a sterically demanding $t$BuBrettPhos ligand and a ligand-preligated 2-aminobiphenyl palladacycle precatalyst. The reaction is not limited to the preparation of deuterated anisoles, as trideuteromethyl vinyl ether were also synthesized from halo-styrenes.

Scheme 71. Pd-catalyzed trideuteromethoxylation of (hetero)aryl halides
Scheme 72. Pd-catalyzed arylation or vinylation of CD$_3$OD

In 2018, Mai and co-workers developed a mild, metal-free para-C–H trideuteromethoxylation of anilides via PIFA-mediated soft-hard acid-base (SHAB)-controlled cross dehydrogenative coupling with CD$_3$OD (Scheme 73).$^{120}$ Both electron-withdrawing and electron-donating anilides were suitable partners. Besides benzoyl anilides, pivaloyl anilides also gave the trideuteromethoxylated products in moderate yields. The authors proposed the formation of the intermediate A from a nucleophilic attack of the anilide on PIFA, followed by the loss of PhI and CF$_3$COO$^-$ to give the nitrenium ion B, which could resonate to the harder carbenium ion C. Finally, a nucleophilic attack of CD$_3$OD delivers the OCD$_3$-incorporating aryl ethers.

Scheme 73. SHAB-controlled para-C–H trideuteromethoxylation of anilides

In addition to the above discussed C(sp$^2$)-trideuteromethoxylation, examples of alkyl trideuteromethoxylation have also been reported. In 2016, Mal and co-workers reported the
synthesis of α-iodo-trideuteromethyl ether via PIDA-I$_2$ mediated vicinal iodoniodetriodeuteromethoxylation of alkenes using CD$_3$OD as the nucleophilic solvent (Scheme 74). Both activated styrenes and unactivated terminal olefin are suitable substrates. The trideuteromethoxylation of the styrene substrates proceeded regioselectively at the benzylic positions due to the formation of a stable benzylic cationic intermediate. Furthermore, 100% diastereoselectivity was observed for the difunctionalization of the cyclic indene substrate, which might be caused by a steric reason. Mechanistically, the reaction of PIDA with I$_2$ first affords an electrophilic IOAc reagent. The addition of iodinium cation (I$^+$) to the double bond generates a bridged iodonium ion via cation-π interaction. The regioselective nucleophilic attack of CD$_3$OD on this cationic intermediate delivers the final product.

Scheme 74. PIDA-I$_2$ mediated iodotrideuteromethoxylation of alkenes with CD$_3$OD

4. Organic Molecules Containing S–CD$_3$ Bond

Methyl thioethers have attracted considerable attention because they are common structural constituents present in many biological and pharmaceutical molecules and can serve as important intermediates. The synthesis of molecules containing an S–CD$_3$ bond is therefore important for biological application but also for mechanism understanding. Like ether bonds, the thioether bonds can be generated by either S–CD$_3$ or C–SCD$_3$ bond formations. However, compared with C/N/O-trideuteromethylation, the examples of S-trideuteromethylation are relatively few.

4.1. S-Trideuteromethylation of Thiophenol Derivatives

In 2019, Wang and Chen successfully prepared a range of trideuteromethyl aryl thioethers via S-trideuteromethylation of the corresponding thiophenols with TDMSOI (Scheme 75). When a free amino group is present in the same molecule, selective S-trideuteromethylation could be achieved.

Scheme 75. One-pot" S-trideuteromethylation of thiophenols with TDMSOI
Besides the above-mentioned N- and O-trideuteromethylation, DMTT was also used for selective S-trideuteromethylation of thiophenols and mercapto-bearing compounds (Scheme 76). Amine and hydroxyl groups remained intact in these reactions.

Scheme 76. S-trideuteromethylation with DMTT

4.2. Formation of C–SCD₃ bond

DMSO often serves as a methyl source, but it can also be a source of methylthiol in organic synthesis. In 2014, Das and co-workers reported the synthesis of γ-substituted β,γ-unsaturated α-ketomethylthioesters from α,β-unsaturated ketomethyl derivatives via PPh₃•HBr-DMSO-mediated methylthioesterification (Scheme 77). When d₆-DMSO was used, the SCD₃-containing product was exclusively formed, suggesting that the methyl group originates from DMSO. Mechanistically, the reaction of PPh₃•HBr with d₆-DMSO affords Br₂ and (CD₃)₂S. α-Bromination of the ketone followed by nucleophilic substitution of the resulting α-bromoketone A with (CD₃)₂S gives the α-SCD₃-substituted intermediate B. Further α-bromination of the intermediate B and subsequent d₆-DMSO-mediated Kornblum oxidation delivers the final trideuteromethylthioesterification product.

Scheme 77. Trideuteromethylthioesterification with PPh₃•HBr/d₆-DMSO and the proposed mechanism

In 2018, Gui and Tan described cobalt-catalyzed, 8-AQ directed highly mono-selective ortho-methylthiolation of benzamides and acrylamides using DMSO as the methylthiolating reagent and PhCOCl as the additive, respectively (Scheme 78). Using d₆-DMSO as the -SCD₃ source, C–H trideuteromethylthiolation of the 8-AQ bearing benzamide was achieved in 76% yield. The reaction starts with the complexation of Co(III)X₂ with the 8-AQ directing group to afford the intermediate A. Intramolecular SET of A followed by Ag(I)-mediated oxidation gives the cation radical Co(III) intermediate C, which reacts with an in-situ generated deuterated methylthio anion (from d₆-DMSO and PhCOCl) to provide the radical intermediate D. A second intramolecular SET of the intermediate D affords the cation intermediate E, which after a deprotonation-protonation process releases the final ortho-SCD₃ product together with Co(II)X₂.
Ag(I)-mediated re-oxidation of Co\textsuperscript{III}X\textsubscript{2} regenerates the catalytically active Co(III) species and closes the catalytic cycle.

Scheme 78. Co-catalyzed ortho-trideuteromethylthiolation of substituted benzamide with \textit{d}_\textit{o}-DMSO

In 2020, Wang and coworkers reported a visible-light-promoted trideuteromethylthiolation/trideuteromethylselenation of aryldiazonium salts using PhSO\textsubscript{2}SCD\textsubscript{3} or PhSO\textsubscript{2}SeCD\textsubscript{3} as the novel deuterated methylation reagents using Eosin Y as photosensitize (Scheme 1).\textsuperscript{125} Trideuteromethyl sulfoxides were also prepared by conducting the reactions in the presence of air instead of nitrogen. The two deuteromethylation reagents were prepared from trideuteromethylsulfoxonium iodide (TDMSOI) which is described earlier for C/N/O/S-trideuteromethylation.\textsuperscript{126} Mechanistically, upon visible-light irradiation of EY gives EY*, SET transfer event with the aromatic diazonium salt generates EY\textsuperscript{+•} and an aryl radical. The latter reacts with PhSO\textsubscript{2}SCD\textsubscript{3} to afford the (methyl-\textit{d}_\textit{o})methylthiolation product together with a sulfone radical. A second SET transfer between EY\textsuperscript{+•} and the sulfone radical regenerates EY to complete the catalytic cycle. In the presence of air, further oxidation of the (methyl-\textit{d}_\textit{o})methylthiolation product with \textit{1}O\textsubscript{2}, which is generated via energy transfer between \textit{3}O\textsubscript{2} and EY*, leads to the corresponding trideuteromethyl sulfoxide product.
Scheme 79. Visible-light-promoted cross-coupling reactions of aryldiazonium Salts with S-methyl-$d_3$ sulfonothioate or Se-methyl-$d_3$ selenium sulfonate

Conclusions

The increasing interest in trideuteromethyl-containing molecules has driven chemists to innovate in their preparation methods. The landscape of the CD$_3$-introduction was initially dominated by functional group interconversion using stoichiometric metallic deuteride. This former approach is now less commonly employed in reduction due to toxicity issues, but it has seen considerable improvement with the advances in catalytic reduction using D$_2$ as safer deuteride sources and the development of catalytic hydrogen borrowing strategies, which employed deuterated solvent such as CD$_3$OD as deuteride surrogate. Such progress has also enabled to build up $N$-CD$_3$ units by reductive amination from deuterated solvents.

The coupling with nucleophilic trideuteromethyl sources is restrained to C–CD$_3$ bond formation and suffered from the low diversity of metallic trideuteromethyl reagents. However, the promising recent success of stable CD$_3$B(OH)$_2$ combined with the popularity of Suzuki-Miyaura cross-coupling reactions has led to considerable development of more efficient catalytic systems to introduce CD$_3$ group. On the other way, the coupling with electrophilic trideuteromethyl sources is an excellent solution to link CD$_3$ unit to organic molecules by either C, N, O, or S atom. The reaction portfolio ranges from classical cross-coupling reaction to C–H bond functionalizations using in most of the cases CD$_3$I, albeit it is an hazardous reagent. Therefore, a new research trend appeared to find safer and easy-to-handle surrogates, such as CD$_3$-OTs, OP(OC$_3$D)$_3$, DMTT, or reagent derived from $d_6$-DMSO. The trideuteromethylation of C–H bonds is the most promising approach for the construction of C–CD$_3$, which is in its early stages.

Several avenues of research remain longstanding synthetic challenges: (1) the discovery of new directing groups able to accelerate and control the site of C–H activation; (2) regiodivergent and remote C–H bond trideuteromethylation; (3) the incorporation of CD$_3$ unit into molecules which do not contain strongly coordinating functional groups; (4) functionalization of non-acidic
C(sp)^3–H and their enantioselective version. These methodologies’ studies may lead the predictive late-stage functionalization of complex pharmaceuticals to access their CD₃-congeners directly.

More recently, alternative radical pathways have emerged as excellent solutions to produce C–CD₃ bonds. These protocols involve the formation of CD₃ radical which latter reacts in Minisci-type reactions for the formal C–H bond alkylation of heteroarenes, or with SOMOphilic groups to afford difunctionalized molecules. The replacement of stoichiometric amount of oxidants by photoredox catalysis for the generation of the CD₃ radical has pave the way to more efficient and eco-friendly protocols increasing further industrial application. However, there is room for improvement in designing safer CD₃ radical precursors and developing novel protocols that redefine the boundaries of radical-based C–H bond functionalization beyond pyridine derivatives.

Regarding the formation of N–CD₃, O–CD₃, and S–CD₃ bonds, trideuterometylation with CD₃-I surrogate is a preferred method. One of the most remaining challenge is when the organic molecules contain several nucleophilic sites able to react with electrophilic trideuteromethyl sources leading to a mixture of CD₃-compounds. Future efforts to design more selective electrophilic trideuteromethyl sources displaying higher functional group tolerance will be necessary for increasing industrial application. Finally, trideuteromethoxylation and trideuteromethylthiolation reactions also offers a solution to introduce OCD₃ and SCD₃ bonds using simple deuterated solvent. A future direction will be to achieve C(sp²)–H and C(sp³)–H bonds trideuteromethoxylation and trideuteromethylthiolation.

With these methodologies in hand, industrially important CD₃-containing molecules are now more accessible than ever. We hope that the inventive strategies discussed herein should provide a resource for the construction of C–CD₃, N–CD₃, O–CD₃, and S–CD₃ bonds. The development of CD₃ sources and cross-coupling conditions will continue and we hope that the chemistry explored in this Review will help for future innovation and drug discovery.

Conflicts of interest

“There are no conflicts to declare”.

Notes and references

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Bibliography

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