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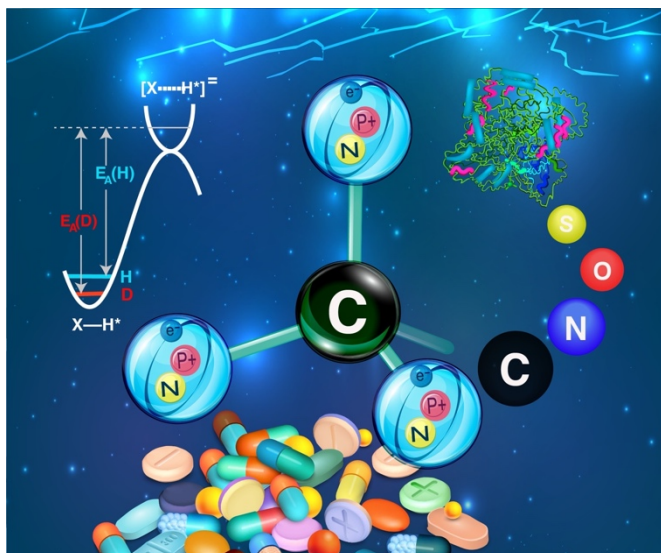
Broadening of Horizons in the Synthesis of CD₃-labeled Molecules

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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. CD₃-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 CD₃ group have been developed. This Review gives an overview of the methods for the preparation of CD₃-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.¹ 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.^{2,3} 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.⁴ The switch from OMe to OCD₃ groups enables to slow 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.⁵ A handful of deuterated compounds, including those containing CD₃ groups instead of CH₃ 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).

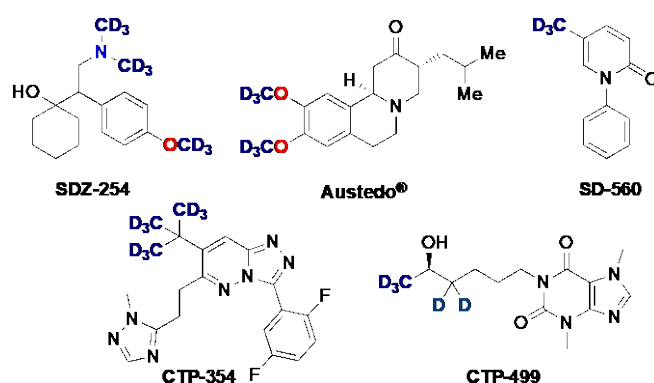


Figure 1. Examples of CD₃-Containing Molecules in Drug Designs.

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,⁶⁻⁸ or D-labeling molecules by H-D exchanges,⁹⁻¹¹ the synthesis of CD₃-labeling molecules, has been less subject to overview reviews.¹² Although the literature abounds in examples of the synthesis of CD₃-containing molecules, no specific methodology dealt exclusively with incorporating the CD₃ 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 CD₃ 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.*, CD₃-C, CD₃-N, CD₃-O, and CD₃-S) and by which type of reaction is employed to create them. For the construction of C-CD₃ 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-CD₃ linkages are often prepared by i) reduction of carbamates, ii) H/D exchanges of methylamine or iii) by N-trideuteromethylation (Figure 2b). The O-CD₃ or S-CD₃ 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), the electrophilic trideuteromethylation reagents (Figure 2F) and the nucleophilic trideuteromethylation reagents or trideuteromethylated radical precursors (Figure 2G). This discussion of innovative strategies developed for various CD₃X-containing molecules should provide chemists with a set of resources and conditions applicable to a range of challenging substrates, including potential pharmaceuticals or agrochemicals.

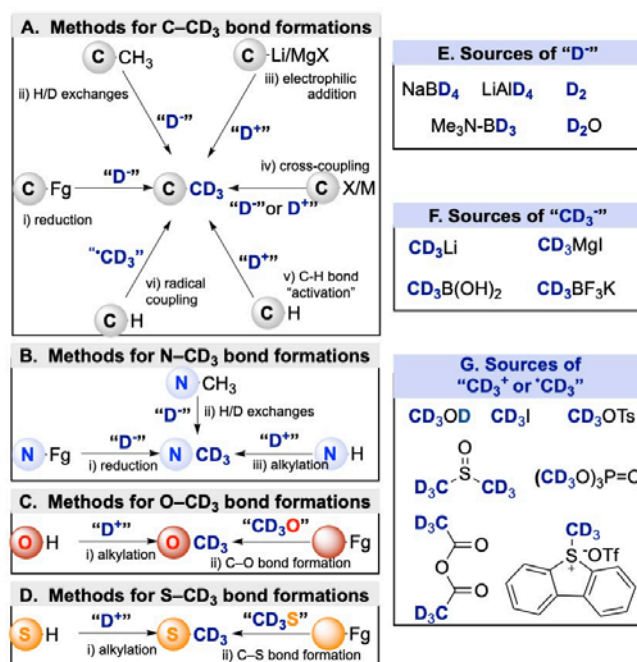


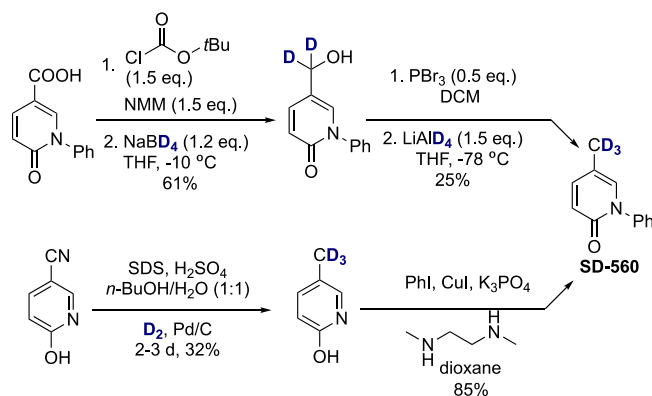
Figure 2. Scope of this Review: **A-D** different Methods for introduction of CD₃ group into organic molecules & **E-G** different trideuteromethyl reagents

1. Organic Molecules Containing C-CD₃ 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.¹³ 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.

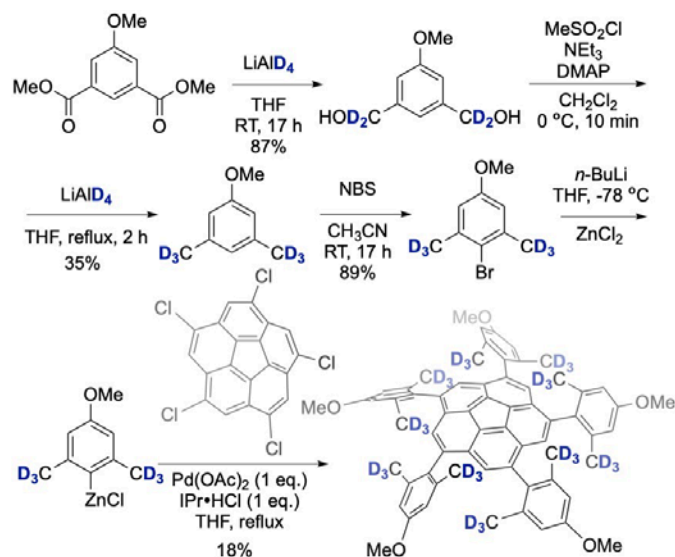
1.1. Reductive Methods

Conventional functional group interconversion is a traditional way to synthesize CD₃-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-CD₃ group (Scheme 1).¹⁴ In the first pathway, the carboxylic acid function of the pyridinone is converted to the CD₃ moiety *via* a sequence of anhydride formation, NaBD₄-mediated reduction, bromination, and LiAlD₄-mediated Br-D exchange (Scheme 1, top). In the second pathway, the reduction of the nitrile group was achieved using highly flammable deuterium gas (D₂) 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).



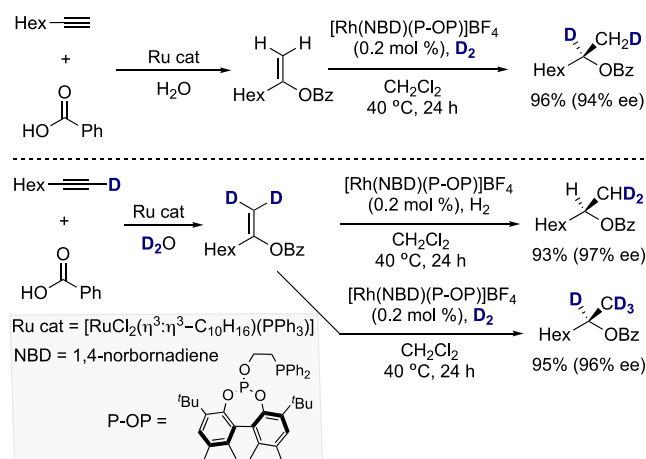
Scheme 1. Introduction of the 5-CD₃ group to **SD-560** by functional group interconversion

In 2008, Siegel 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).¹⁵ The CD₃ group in the Negishi reagent was synthesized in a two-step procedure from the corresponding methyl ester *via* LiAlD₄-mediated reduction followed by mesylation, and LiAlD₄-mediated OMs-D exchange.



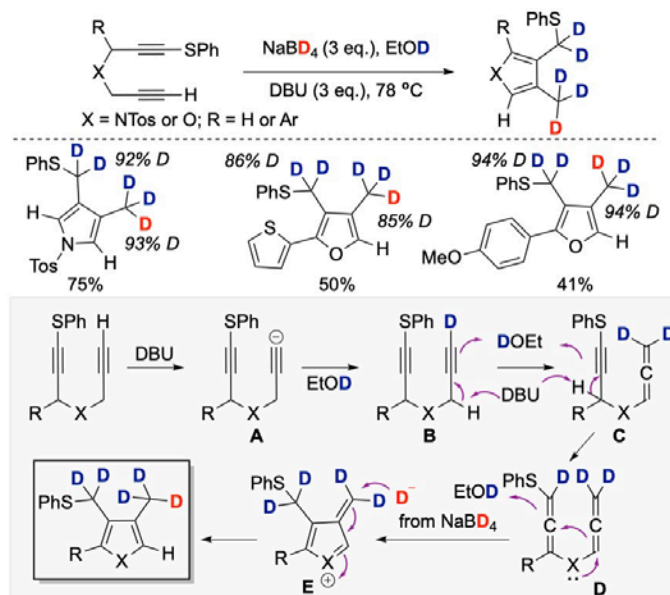
Scheme 2. Synthesis of deuterated pentaarylcorannulene

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 CDH₂-, CD₂H-, or CD₃-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).¹⁶ The nondeuterated and deuterated vinyl benzoates were prepared by Ru-catalyzed addition of benzoic acid to (deuterated) oct-1-yne in the presence of H₂O or D₂O, respectively. The hydrogenation of those deuterated vinyl benzoates was carried out using a chiral Rh(I) complex with D₂ gas to afford the CD₃-labeled 2-octyl benzoates.



Scheme 3. Enantioselective synthesis of CDH_2 -, CD_2H -, or CD_3 -labeled 2-octyl benzoates via asymmetric hydrogenation/deuteration

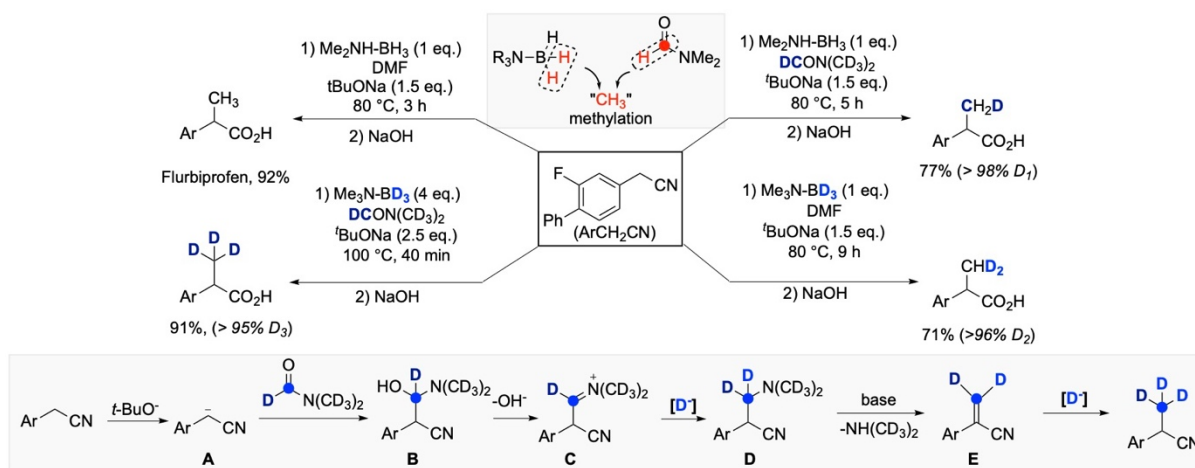
In 2015, Yoshimatsu and co-workers completed the synthesis of trideuteromethylated pyrroles and furans *via* metal-free deuterative cyclization of *N*- or *O*-tethered sulfanyl 1,6-diynes in the presence of $\text{NaBD}_4/\text{EtOD}$ (Scheme 4).¹⁷ The deuteration regioselectively occurs at the methylene 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 α -monomethylation of arylacetonitriles and arylacetamides using $\text{R}_3\text{N-BH}_3/\text{DMF}$ system as an *in-situ* methyl source (Scheme 5).¹⁸ 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 $\text{R}_3\text{N-BH}_3$. By

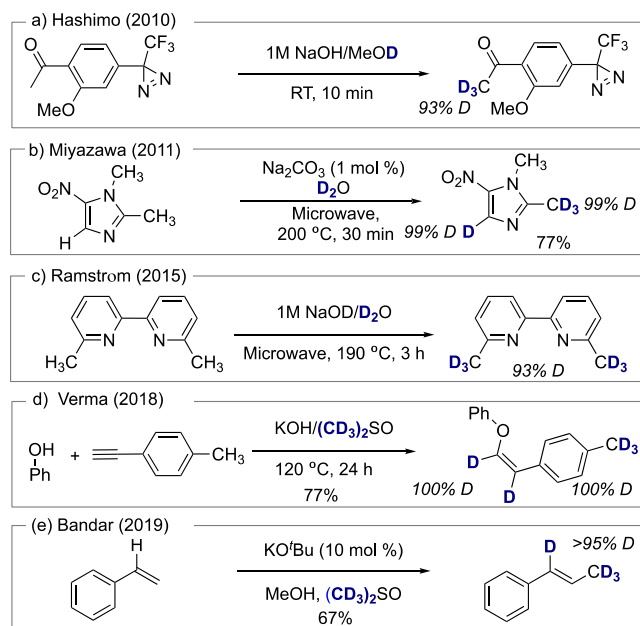
tuning the corresponding deuterium sources, the reaction system enables selective incorporation of CDH₂, CD₂H, and CD₃ moieties using Me₂NH-BH₃/*d*₇-DMF, Me₃N-BD₃/DMF, and Me₃N-BD₃/*d*₇-DMF systems, respectively. They showed the synthetic utility of the methylation method with the synthesis of anti-inflammatory flurbiprofen and its deuterium-labeled derivatives. The α -trideuteromethylation is initiated by the deprotonation of the very acidic benzylic C(sp³)-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 (CD₃)₂NH from the intermediate **D**, the resulting acrylonitrile **E** undergoes further deuteride reduction to afford the final C-CD₃ product.



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

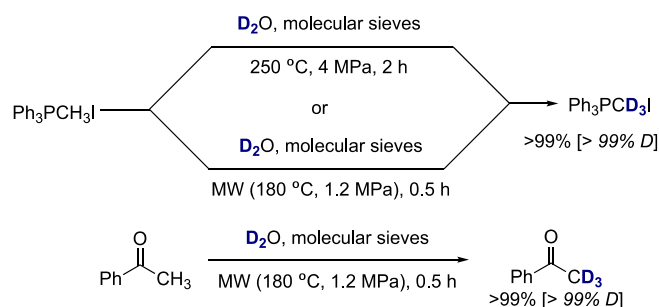
1.2. H-D Exchange of Acidic Methyl Groups

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.^{19, 20} 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/D₂O,^{21, 22} Na₂CO₃/D₂O,^{23, 24} NaOH/MeOD,²⁵ KOtBu/DMSO-*d*₆,²⁶⁻²⁸ and KOH/DMSO-*d*₆²⁷ have been employed in the deuteration of (hetero)aryl, allyl and acetophenone methyl groups (Scheme 6).



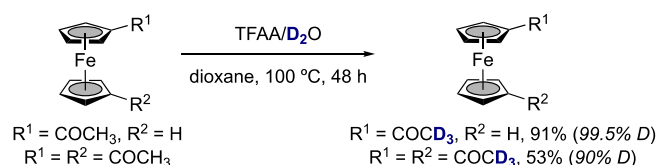
Scheme 6. Selected examples of base-promoted H-D exchanges

Matsubara and co-workers demonstrated that molecular sieve could also serve as a weak solid base in α -deuteration of Wittig salts and acetophenone with D_2O (Scheme 7).²⁹



Scheme 7. Molecular sieve-catalyzed hydrothermal H-D exchange of Wittig salts and acetophenone

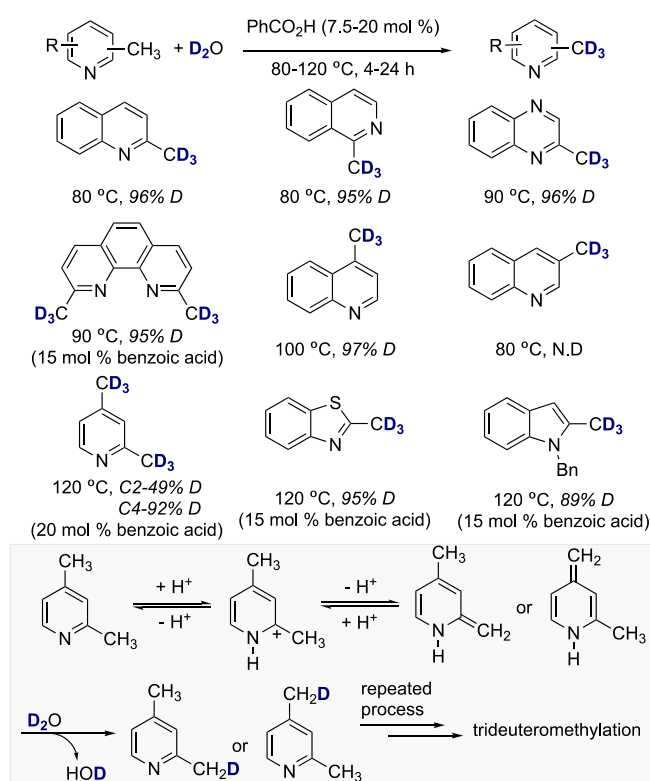
Compared with base-catalyzed H-D exchanges, the examples of acid-catalyzed H-D exchange are fewer. In 2005, Evchenko and co-workers reported trifluoroacetic anhydride (TFAA)-catalyzed H-D exchange of acetylferrocenes using D_2O as the deuterium source (Scheme 8).³⁰ The deuterium incorporation selectively occurred at the acetyl group without the interference of the cyclopentadienyl ring protons.



Scheme 8. TFAA-catalyzed H-D exchange of acetylferrocenes

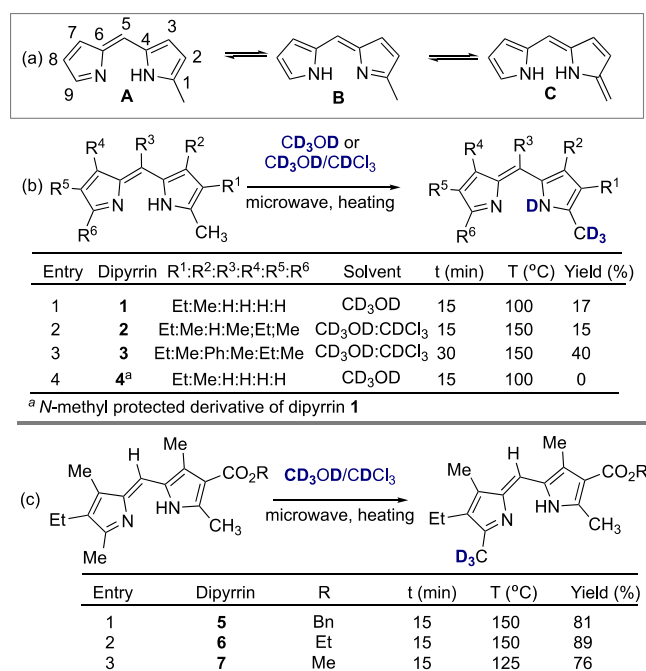
In 2017, Yin and co-workers reported benzoic acid-catalyzed regioselective deuteration of the methyl groups of *N*-heteroarylmethanes using D_2O as the deuterium source (Scheme 9).³¹ The deuteration was observed at the 2- or 4-methyl groups of *N*-heteroarylmethanes, whereas no

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 D₂O delivers the deuteriomethylated heteroarenes.



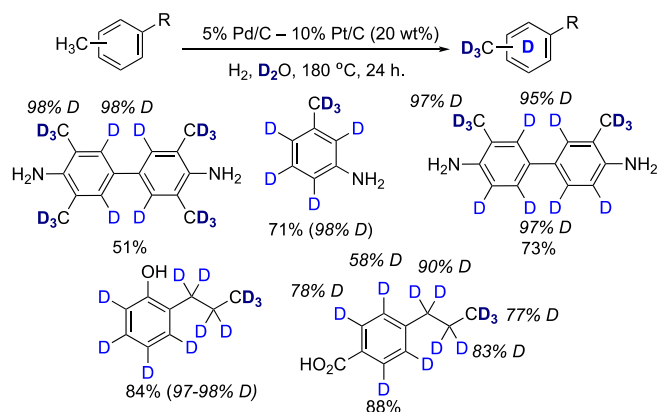
Scheme 9. Brønsted acid-catalyzed deuteration at methyl groups of *N*-heteroarylmethanes and proposed mechanism

In 2017, Thompson and co-workers reported the synthesis of trideuteromethylated dipyrrens *via* microwave-promoted deuterium exchanges at the 1-methyl group of dipyrrens using CD₃OD or mixed CD₃OD/CDCl₃ as the deuterium source without using either acid nor base.³² The deuteration of 1-methyl substituted dipyrren 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 dipyrrens **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 dipyrren **4** failed to participate in the deuteration since the critical dipyrren *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 dipyrrens regioselectively occurred at the α -methyl group distal from the electron-withdrawing group (Scheme 10.c).



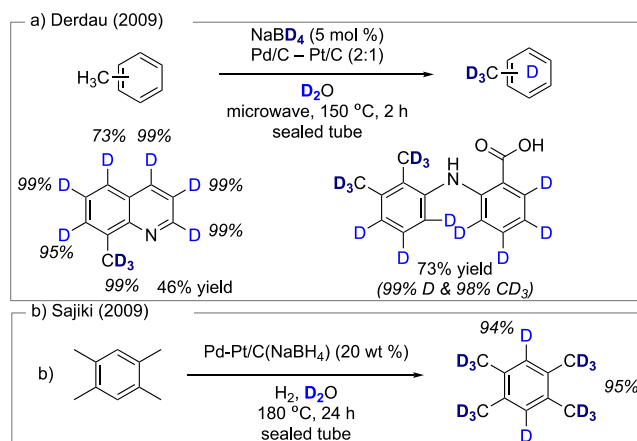
Scheme 10. MW-assisted heat-mediated H-D exchange of 1-methyl dipyrins

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 D₂O 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(sp³)-H benzylic bonds, along with the less acidic C(sp²)-H bond affording fully deuterated aromatic derivatives.



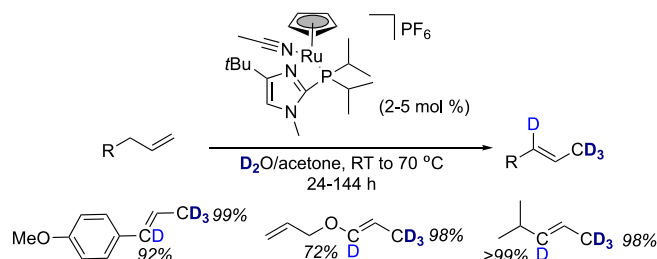
Scheme 11. Multiple deuterations of arenes using the Pd/C-Pt/C-D₂O-H₂

In 2009, Deraud and co-workers reported the use of a NaBD₄-activated Pd/C and Pt/C catalyst mixtures in highly efficient global deuteration of 8-methylquinoline and mefenamic acid using D₂O 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 NaBH₄-activated Pt/Pd/C catalytic system was utilized by Sajiki and co-workers in multiple deuterations of 1,2,4,5-tetramethylbenzene in D₂O (Scheme 12.b).³⁵ Besides the methyl groups, the highly hindered C3 and C6-aromatic hydrogens were also efficiently deuterated.



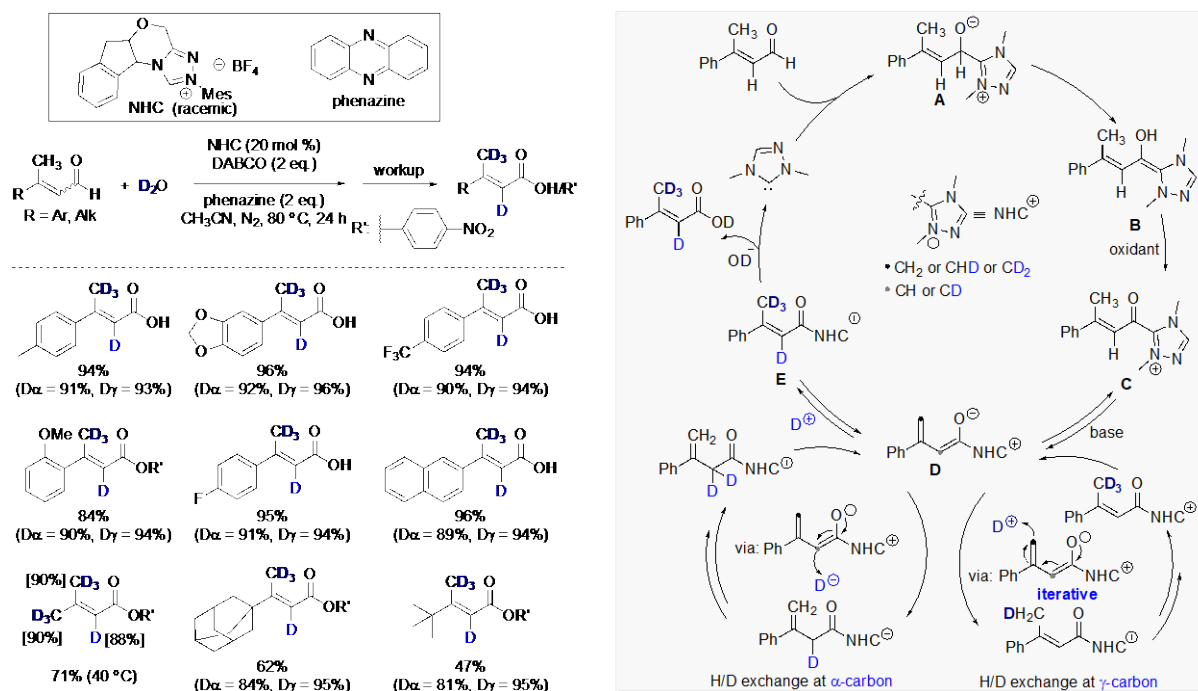
Scheme 12. H-D exchange using NaBD₄-activated Pd/Pt/C as catalyst in D₂O

In 2009, selective vinyl and allylic C–H bond labeling of various alkenes were achieved by Grotijahn 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

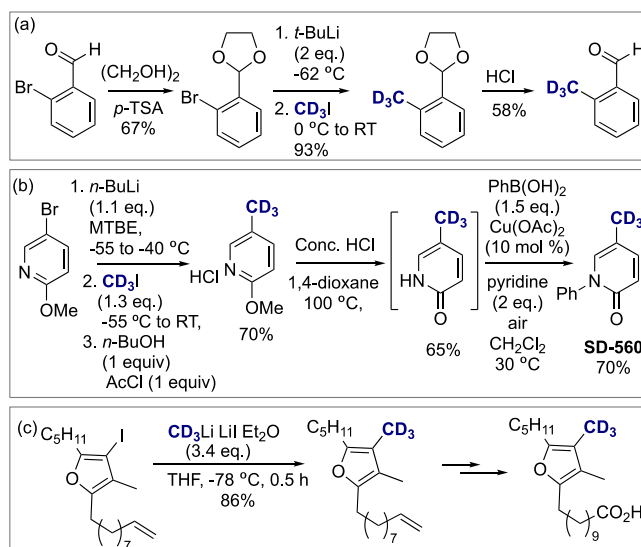
Organocatalysts could also promote the H-D exchange. In 2020, Chi and co-workers disclosed an early example of NHC carbene-catalyzed H-D exchanges of enals at allylic C(sp³) and C(sp²) sites using D₂O as the deuterium source (Scheme 14).³⁷ With an aminoindanol-derived NHC as precatalyst, DABCO as base 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-catalyzed synthesis of α -D- β -CD₃ substituted 2-alkenoic acids/esters via H-D exchange of enals with D₂O and the proposed mechanism

1.3. Halogen/Metal Exchange

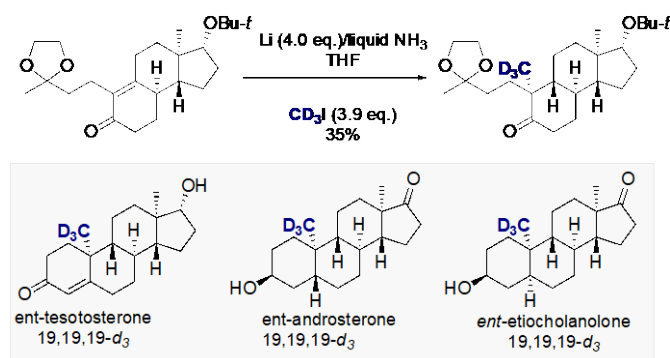
The aromatic metalation is a valuable protocol for the construction of well-decorated (hetero)arenes. Aromatic lithiation is carried out by lithium–hydrogen or lithium–halogen exchange. Once generated, the aryllithiums react with external electrophiles, CD₃I in this case, to afford the C-CD₃ functionalized (hetero)arenes. Since organolithium reagents are highly nucleophilic, additional protection and deprotection sequences are required for compounds bearing sensitive groups (Scheme 15.a).³⁸ The synthesis of **SD-560** through lithium–halide exchange strategy demonstrated its synthetic utility.¹⁴ As shown in Scheme 15.b, metalation of the bromopyridine with *n*-BuLi followed by trideuteromethylation with CD₃I successfully introduces the CD₃ group. Interestingly, the halogen-CD₃ exchange was also directly carried out from CD₃Li rather than the mixture of *n*-BuLi and iodomethane-*d*₃. The aryl lithium formed could be trapped by the *in-situ* generated CD₃I to afford the trideuteromethylated arene. For example, in 2015, CD₃Li-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).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.^{40, 41} 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).⁴² Subsequent ketal deprotection and adol reaction gave *ent*-testosterone-19,19,19-*d*₃, which was then converted into the GABA_A receptor potentiators *ent*-androsterone-19,19,19-*d*₃ and *ent*-etiocholanolone-19,19,19-*d*₃ using established literature procedures.^{43, 44}

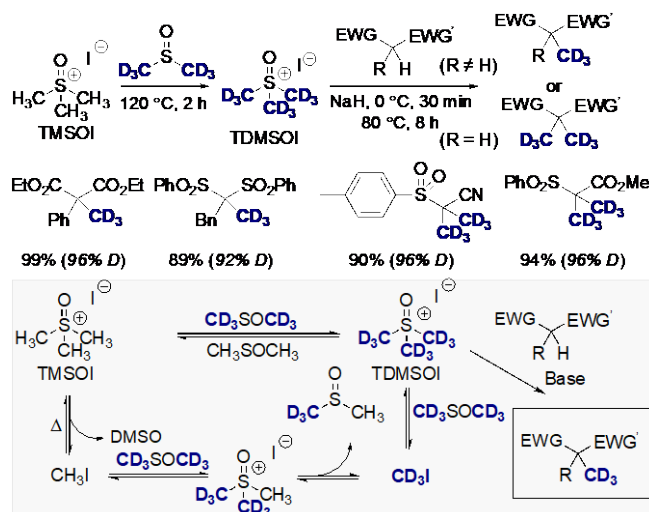


Scheme 16. Synthesis of 19-trideuterated *ent*-testosterone, *ent*-androsterone and *ent*-etiocholanolone using CD₃I

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., *d*₆-DMSO, CD₃OD) by either premodification or *in-situ* hydrogen borrowing.

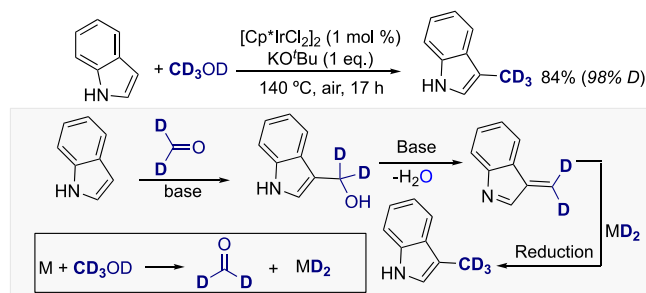
In 2019, Chen and Wang developed a new trideuteromethylation reagent trideuteromethyl sulfoxonium iodide (TDMSOI) for "one-pot" C-trideuteromethylation of active methylene

compounds (Scheme 17).⁴⁵ As a safer alternative to the commonly used CD_3I and $(\text{CD}_3)_2\text{SO}_4$, 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_3I . CH_3I reacts with d_6 -DMSO to form a mixed sulfoxonium, which undergoes a second decomposition to give CD_3SOCH_3 and CD_3I . The final combination of CD_3I with d_6 -DMSO affords TDMSOI, which reacts with active methylene compounds to provide either the *mono*- or double *C*-trideuteromethylated products.



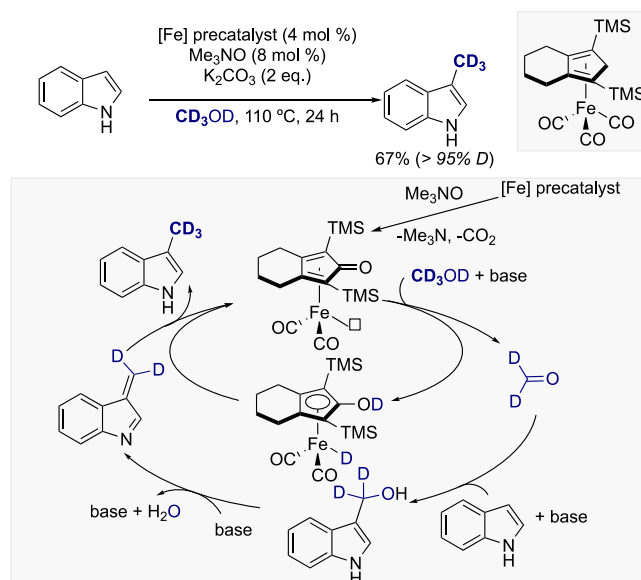
Scheme 17. *C*-trideuteromethylation of acidic C–H bond with TDMSOI

In 2015, Cai and co-workers reported the use of CD_3OD in $[\text{Cp}^*\text{IrCl}_2]_2$ -catalyzed C3-trideuteromethylation of indole with the *in-situ* formation of trideuteromethylation source surrogate through hydrogen borrowing strategy (Scheme 18).⁴⁶ 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_3OD 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)-3*H*-indole intermediate, which is reduced by the metal deuteride to give the final C3-trideuteromethylated indole.



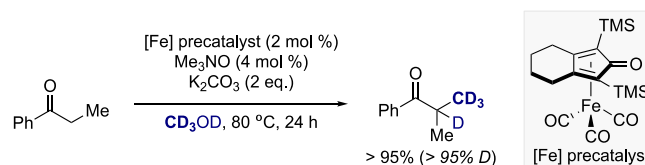
Scheme 18. $[\text{Cp}^*\text{IrCl}_2]_2$ -catalyzed C3-trideuteromethylation of indole with CD_3OD and proposed mechanism

Morrill and co-workers reported a similar procedure for the preparation of *d*₃-skatole, albeit they employed Knölker-type (cyclopentadienone)iron carbonyl complex.⁴⁷ As outlined in Scheme 19, the reaction begins with Me₃NO-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.



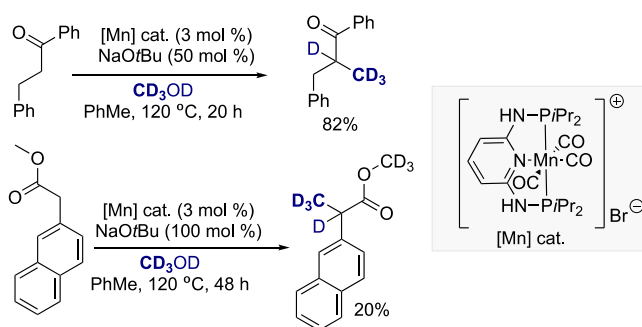
Scheme 19. Fe-catalyzed C3-trideuteromethylation of indole with CD₃OD and proposed mechanism

Knölker-type Fe complex also catalyzes the trideuteromethylation of propiophenone with CD₃OD to afford the α-D, α-CD₃-substituted ketone derivative in more than 95% yield with a high level of D-incorporation (Scheme 20).⁴⁷ 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 α-(D, CD₃)-substituted product together with the catalytically active Fe species.



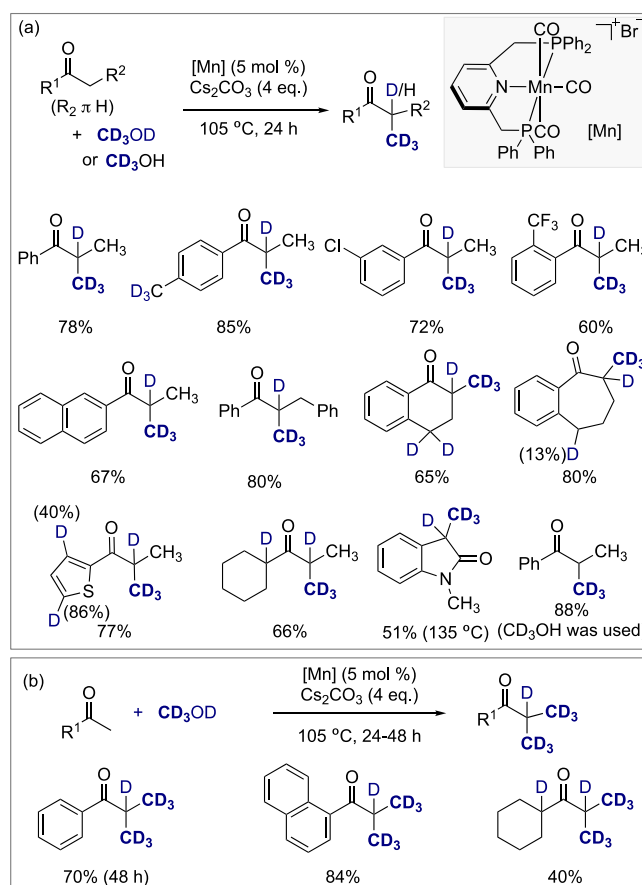
Scheme 20. Fe-catalyzed α-deuteration-α-trideuteromethylation of ketone with CD₃OD

In 2019, Sortais and co-workers reported the first Mn-catalyzed α-methylation of ketones and esters with methanol *via* hydrogen borrowing strategy using a manganese catalyst possessing a 2,6-diaminopyridine backbone (Scheme 21).⁴⁸ By replacing MeOH with CD₃OD, α-deuterated-α-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 α-trideuteromethylated ester is due to the difficulty with isolation.



Scheme 21. Mn-catalyzed α -deuteration- α -trideuteromethylation of ketone and ester with CD_3OD

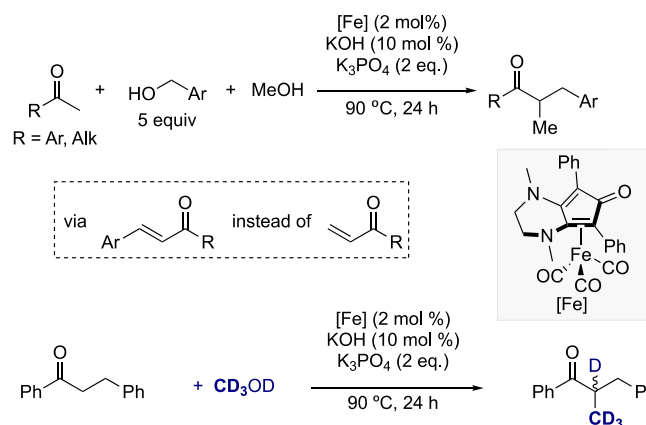
The same year, Rueping and co-workers reported Mn-catalyzed α -deuteration- α -trideuteromethylation of ketones with CD_3OD using air- and moisture-stable aromatic and cationic diphenylphosphine-based Mn-complex, with water being produced as the sole by-product (Scheme 22).⁴⁹ A range of ketones, including propiophenones and cyclic, heteroaromatic, and aliphatic ketones, was trideuteromethylated. When CD_3OH was used instead of CD_3OD , 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.



Scheme 22. Mn-catalyzed α -trideuteromethylation or double trideuteromethylation of ketones with $\text{CD}_3\text{OD}/\text{CH}_3\text{OD}$

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 dihydrochalcone and CD₃OD, which has led to a CD₃-labeled ketone with full deuterium incorporation at the α -carbonyl position.

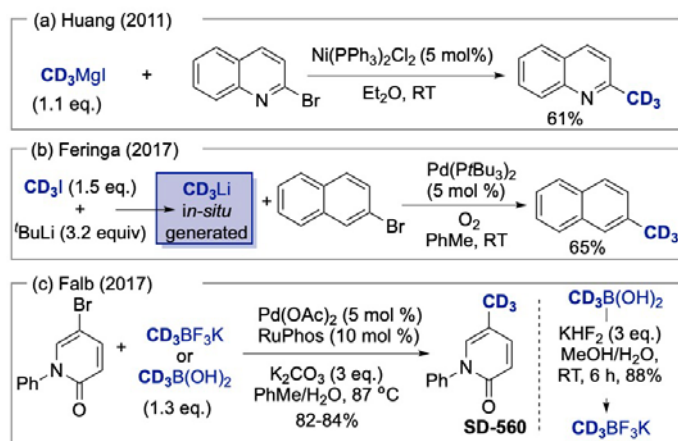


Scheme 23. Tandem three-component alkylation of ketones and mechanistic study

1.5. Transition Metal-Catalyzed Cross-Coupling Reaction

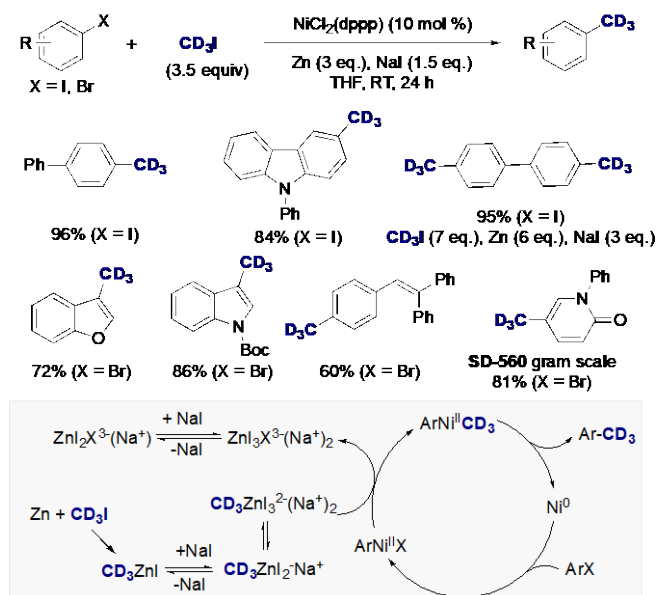
Transition-metal-catalyzed cross-coupling reactions have emerged over recent decades as favored route for swift construction of C(sp²)-C(sp²) or even C(sp²)-C(sp³) bonds in both chemical industry and academia.⁵¹ Such methodologies have become the choice of carbon-carbon bond forming methodology over 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(sp²)-CD₃ 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 [CD₃M] or (2) (hetero)aryl-metal and electrophilic trideuteromethyl reagents.

Several CD₃ organometallic reagents, like CD₃MgI, CD₃Li, CD₃B(OH)₂, and CD₃-BF₃K, have been successfully utilized in such cross-couplings. In 2011, CD₃MgI was used by Huang and co-workers in Ni(PPh₃)₂Cl₂-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 CD₃Li from CD₃I and ^tBuLi 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, CD₃B(OH)₂ and CD₃-BF₃K were used by Falb and co-workers in Pd-catalyzed Suzuki-Miyaura methylation with 5-bromo-1-phenylpyridin-2(1*H*)-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 CD₃B(OH)₂ used in this study is commercially available, and CD₃BF₃K had been prepared with inexpensive KHF₂.



Scheme 24. Transition metal-catalyzed cross-coupling of (hetero)aryl halides with CD_3 organometallic reagents

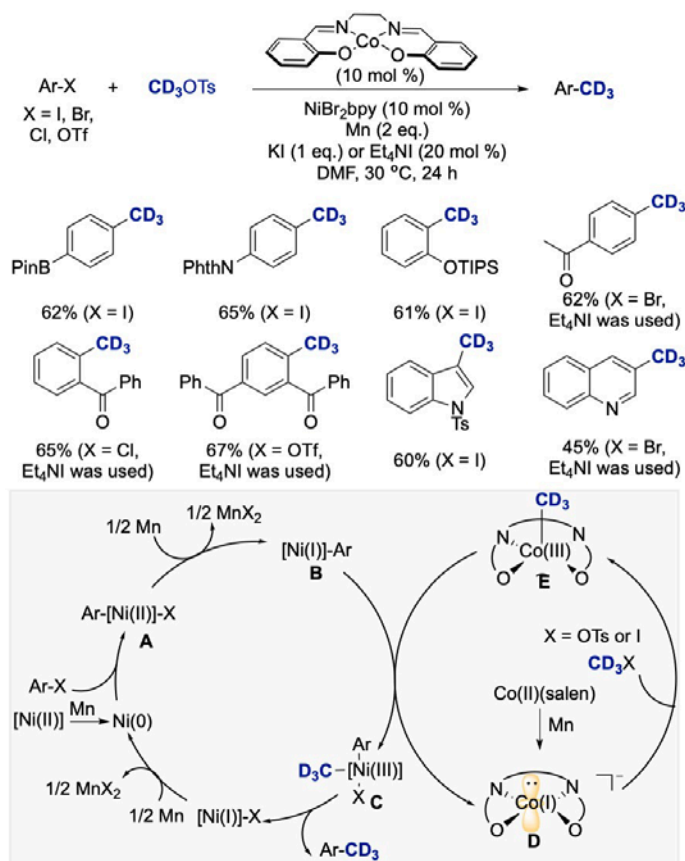
Most of these deuterated methylmetallic reagents are either unavailable or available at a prohibitively expensive cost. To overcome such limitations, in 2016, Liao and co-workers reported the synthesis of trideuteromethylated arenes *via* Ni-catalyzed reductive cross-coupling of (hetero)aryl halides with CD_3I (Scheme 25).⁵⁴⁻⁵⁶ 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 $\text{Ni}^0/\text{Ni}^{\text{II}}$ catalytic cycle where transmetalation between $\text{ArNi}^{\text{II}}\text{X}$ and $\text{CD}_3\text{ZnI}_3^{2-}(\text{Na}^+)^2$ is involved.



Scheme 25. Ni-catalyzed reductive cross-coupling of (hetero)aryl halides with CD_3I and the proposed mechanism

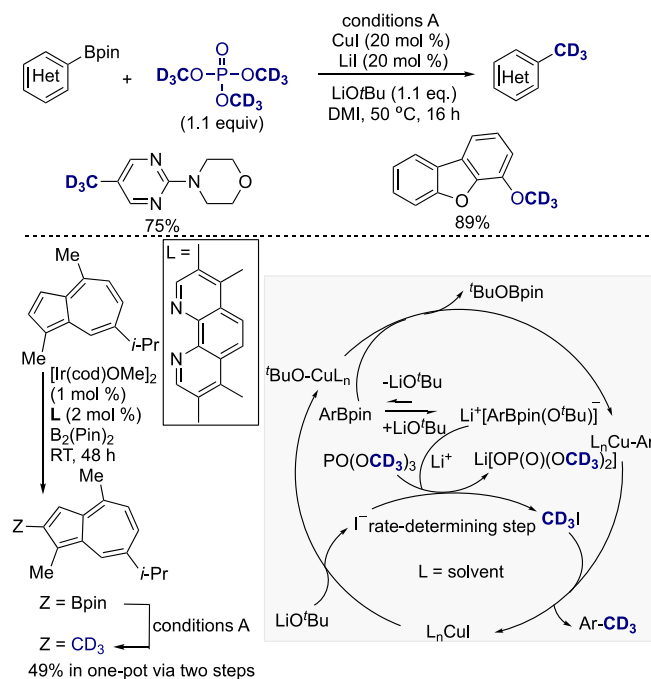
In 2018, Komeyama and co-workers disclosed the use of CD_3OTs in Ni/Co(salen)-catalyzed reductive cross-coupling with (hetero)aryl halides (Scheme 26).⁵⁷ Iodide additives such as KI (for aryl iodide) and Et_4NI (for aryl chloride, bromide, and tosylate) are needful. The authors suggested that the addition of iodide salts promote the generation of CD_3I from CD_3OTs 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 CD₃OTs with the nucleophilic [Co(I)] catalyst **D** affords the CD₃-[Co(III)] intermediate **E**. A single electron transfer-mediated transmethylation between **B** and **E** gives the high-valent Ar-[Ni(III)X]-CD₃ intermediate **C** along with regeneration of the catalytically active [Co(I)] species. Upon reductive elimination, the intermediate **C** releases the CD₃-arene product and [Ni(I)]-X species; the latter undergoes Mn-mediated reduction to regenerate the [Ni(0)] catalyst.



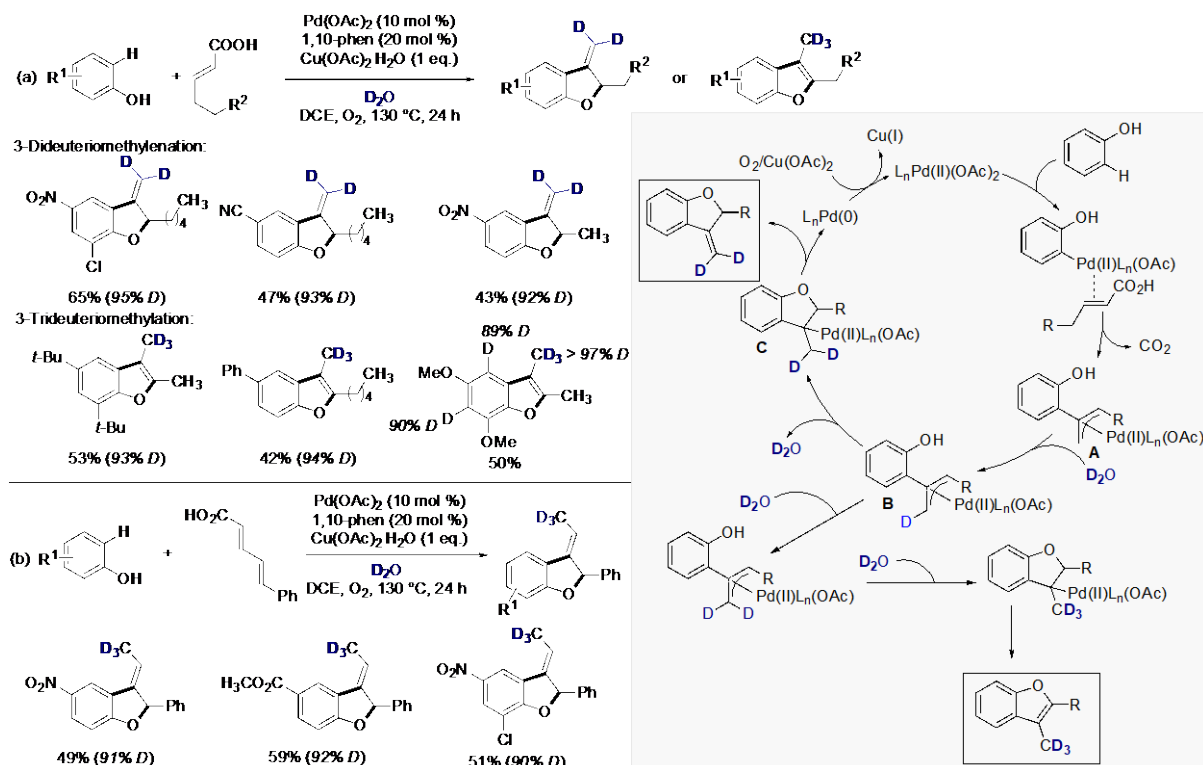
Scheme 26. Ni/Co(salen)-catalyzed reductive cross-coupling of (hetero)aryl halides with CD₃OTs

In 2018, Hartwig and co-workers reported the use of PO(OCD₃)₃ for the trideuteromethylation of (hetero)aryl pinacolboronic esters using CuI and LiI as a dual catalytic system and LiO^tBu 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(OCD₃)₃ serves as an indirect CD₃ source in this reaction. In fact, the actual methylating agent is CD₃I, which is slowly released from iodide and PO(OCD₃)₃. The reaction of CuI with LiO^tBu affords ^tBuO–Cu species, which undergoes transmetalation with ArBpin to give arylcopper species. Meanwhile, ArBpin also reacts with LiO^tBu to form the Li[ArBpin(O^tBu)] boronate complex. The sequestered O^tBu in this complex becomes less nucleophilic and thus unreactive toward CD₃I. Furthermore, the loosely bound Li⁺ in the complex serves as a Lewis acid to catalyze the slow formation of CD₃I from PO(OCD₃)₃ and iodide. Finally, the slowly released CD₃I rapidly reacts with the arylcopper intermediate to afford the desired trideuteromethylated product.



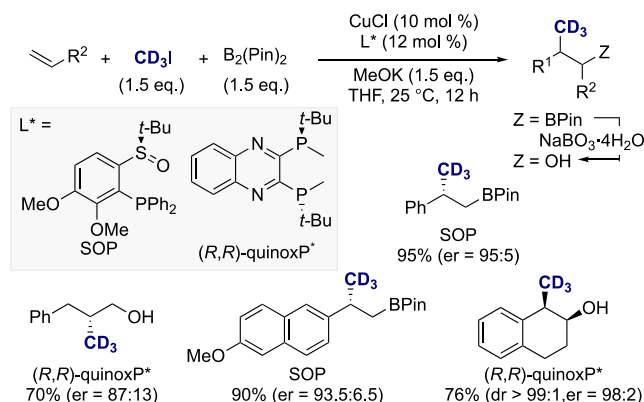
Scheme 27. Copper and iodide co-catalyzed cross-coupling of (hetero)aryl pinacolboronic esters with $\text{PO}(\text{OCD}_3)_3$ and the proposed mechanism

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).⁵⁹ 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-phenylpenta-2,4-dienoic acid. Interestingly, with the addition of D_2O , 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.



Scheme 28. Pd-catalyzed the synthesis of deuterated benzofurans and proposed mechanism

In 2018, Liao and co-workers reported enantioselective Cu-catalyzed trideuteromethylboration of styrenes and unactivated aliphatic olefins using CD_3I in the presence of bis(pinacolato)diboron (B_2Pin_2) (Scheme 29).⁶⁰ 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 alkylcuprate with CD_3I .

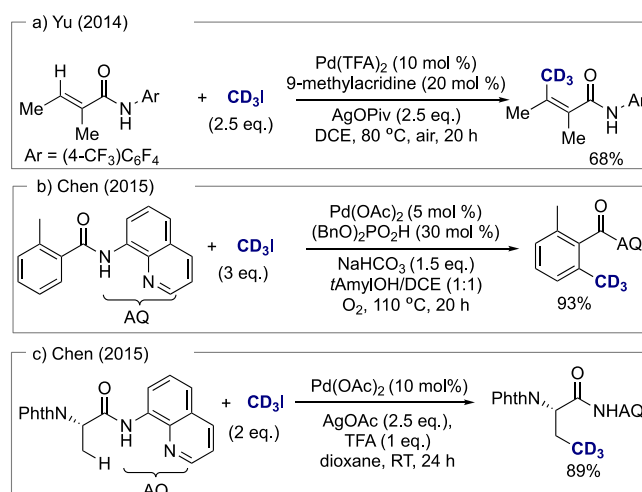


Scheme 29. Cu-catalyzed trideuteromethylboration of alkenes with CD_3I and B_2Pin_2

1.6. Transition-Metal-Catalyzed C–H Bond Trideuteromethylation

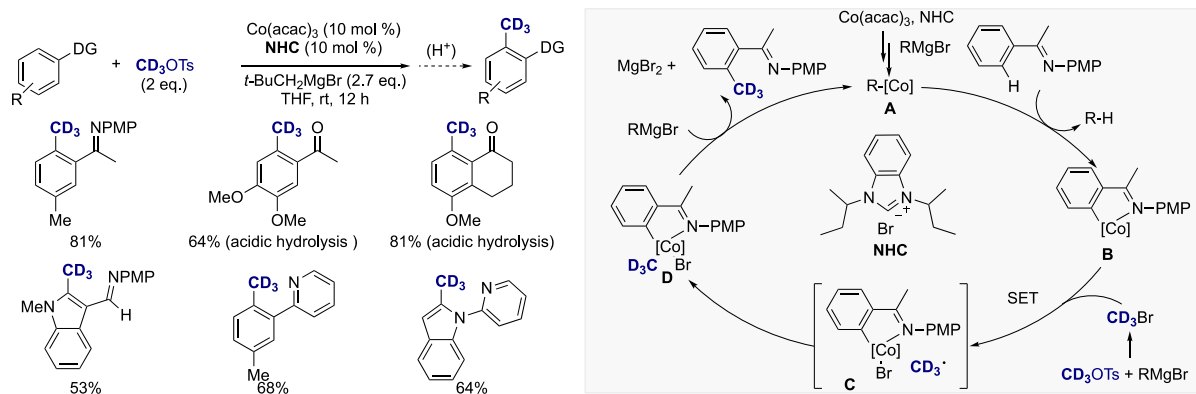
In the past two decades, transition metal-catalyzed C–H bond functionalization has become a suitable atom- and step-economical alternative to cross-coupling reactions owing to prefunctionalization is not required and they did not generate metal salts as waste.⁶¹⁻⁶⁴ When these reactions are performed with trideuteromethyl precursors, 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



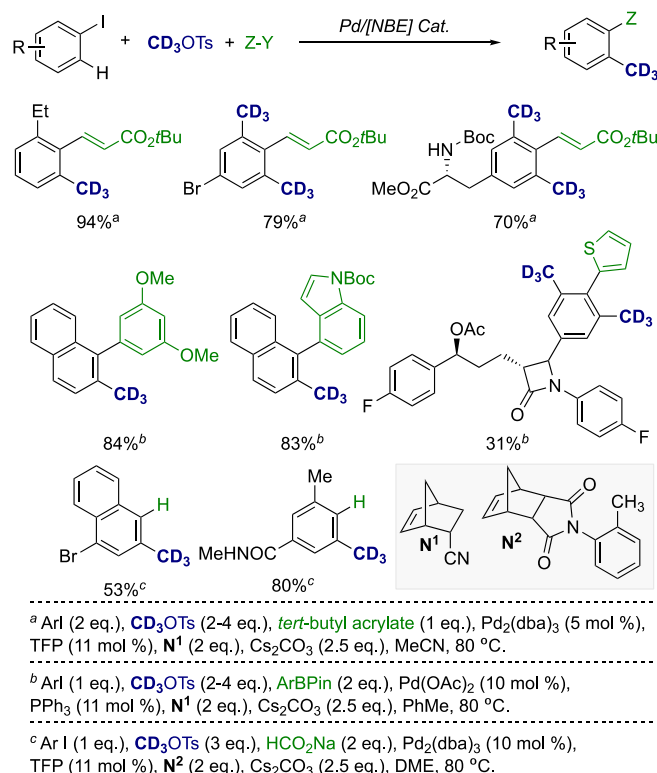
Scheme 30. Pd-catalyzed C(sp²)–H trideuteromethylation with CD₃I

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 cobaltacycle species **B**. SET from the cobalt center to the *in-situ* formed CD₃Br generates a pair of oxidized cobaltacycle 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**.



Scheme 31. Co-catalyzed directed *ortho*-trideuteromethylation of arenes with CD_3OTs and proposed mechanism

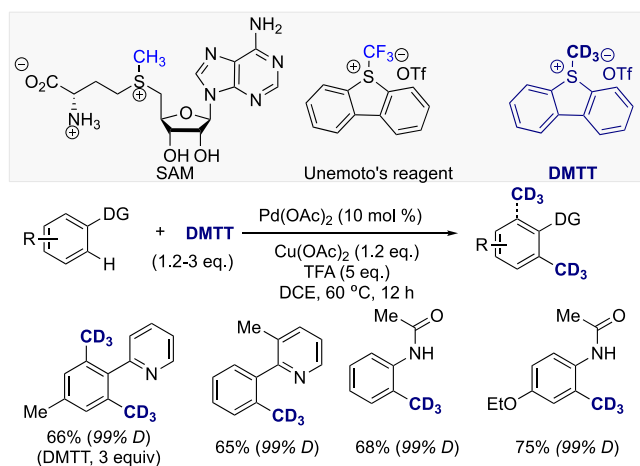
Soon after, CD_3OTs was used by Zhou and co-workers in Catellani-type dual-tasked C–H trideuteromethylation of aryl iodides (Scheme 32).^{69, 70} Diverse *ortho*-trideuteromethylated derivatives were synthesized by terminating the reaction with Heck, Suzuki, or hydrogenation reaction. The applicability 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_3OTs , the corresponding double trideuteromethylation products are obtained.



Scheme 32. Pd-catalyzed Catellani-type C–H bond trideuteromethylation

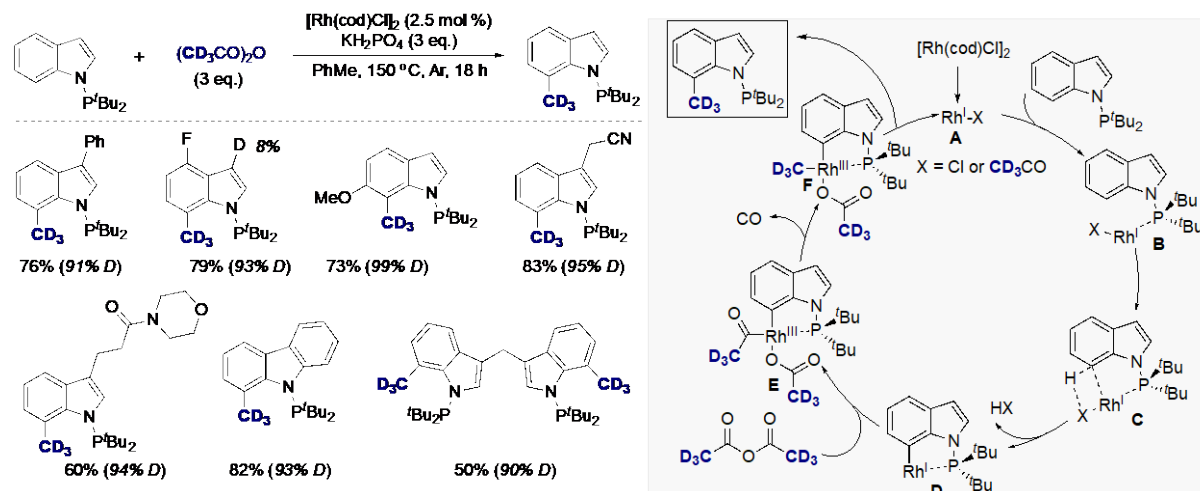
Inspired by radical transferase *S*-adenosylmethionine (SAM) and the design principle of Umemoto's reagent, Shi and co-workers developed a biomimetic methylating agent DMTT (5-(methyl-*d*₃)-5*H*-dibenzo[*b,d*]thiophen-5-ium trifluoromethane sulfonate) for mild and selective

trideuteromethylation of various nucleophiles (Scheme 33).⁷¹ DMTT is easily prepared as a bench-stable solid from dibenzo[*b,d*]thiophene and CD₃OD. This reagent is utilized in Pd-catalyzed pyridine- or acetylamino-directed *ortho*-C(sp²)-H *mono*- or *di*-methylation of several organic and drug molecules.



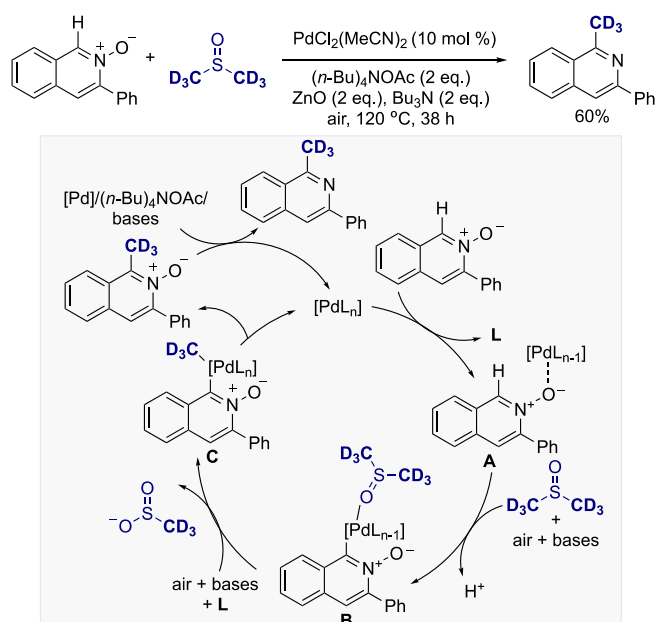
Scheme 33. Pd-catalyzed C–H trideuteromethylation with DMTT

In 2019, Shi and co-workers reported the use of *d*₆-Ac₂O in Rh-catalyzed, indole *N*-P^tBu₂-directed C7-selective C–H trideuteromethylation of indoles (Scheme 34).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. *N*-P^tBu₂ 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 α-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^I-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 *d*₆-Ac₂O onto the rhodacycle affords the Rh^{III} intermediate **E**, which after decarbonylation and reductive elimination produces the final trideuteromethylated product and regenerates the catalytically active species **A**.



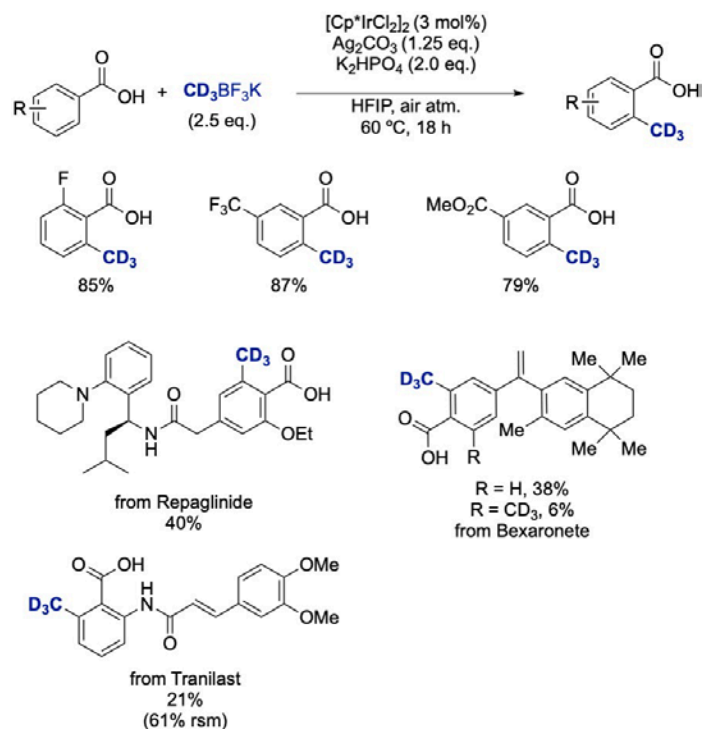
Scheme 34. Rh-catalyzed C7-trideuteromethylation of indoles with *d*₆-Ac₂O and proposed mechanism

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 $(n\text{-Bu})_4\text{NOAc}/\text{ZnO}/\text{Bu}_3\text{N}/\text{air}$ (Scheme 35).⁷³ The trideuteromethylation occurred together with N–O cleavage to afford 1-(methyl- d_3)-3-phenylisoquinoline in 60% yield. $(n\text{-Bu})_4\text{NOAc}$ serves as the phase-transfer catalyst and acts as a base to reduce the N–O bond. Meanwhile, the combination of $\text{ZnO}/\text{Bu}_3\text{N}$ also serves as a base to improve the N–O bond's cleavage. In terms of the reaction mechanism, the coordination of $[\text{PdL}_n]$ 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 $\text{CD}_3\text{S}(\text{O})\text{O}^-$. Reductive elimination of the intermediate **C** and $[\text{PdL}_n]/\text{PTC}/\text{bases}$ -mediated N–O reduction of the resulting trideuteromethylated isoquinoline *N*-oxide gives the final 1- CD_3 -substituted isoquinoline.



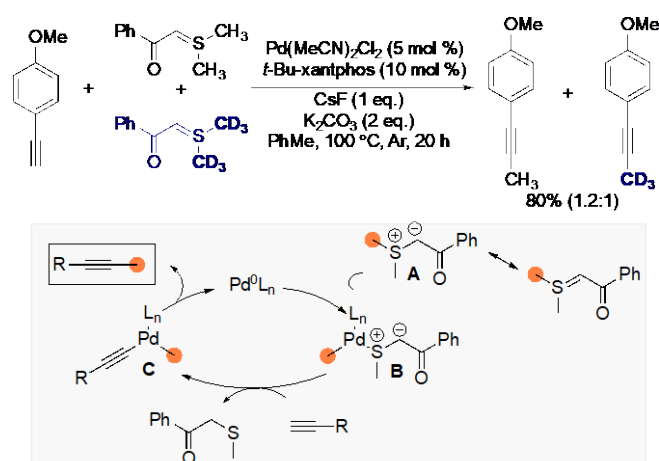
Scheme 35. Pd-catalyzed C–H trideuteromethylation of isoquinoline *N*-oxide with d_6 -DMSO and proposed mechanism

In 2021, Johansson and Martín-Matute reported the use of MeBF_3K and $\text{CD}_3\text{BF}_3\text{K}$ in $[\text{Cp}^*\text{IrCl}_2]_2$ -catalyzed directed *ortho* C–H methylation and trideuterodmethylation of benzoic acids.⁷⁴ 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. $\text{CD}_3\text{BF}_3\text{K}$ used in this study was prepared using the procedure reported by Falb and coworkers.⁷⁵ 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.



Scheme 36. Ir-catalyzed trideuteromethylation of benzoic acids with $\text{CD}_3\text{BF}_3\text{K}$

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).⁷⁶ 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 Pd^0L_n 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.

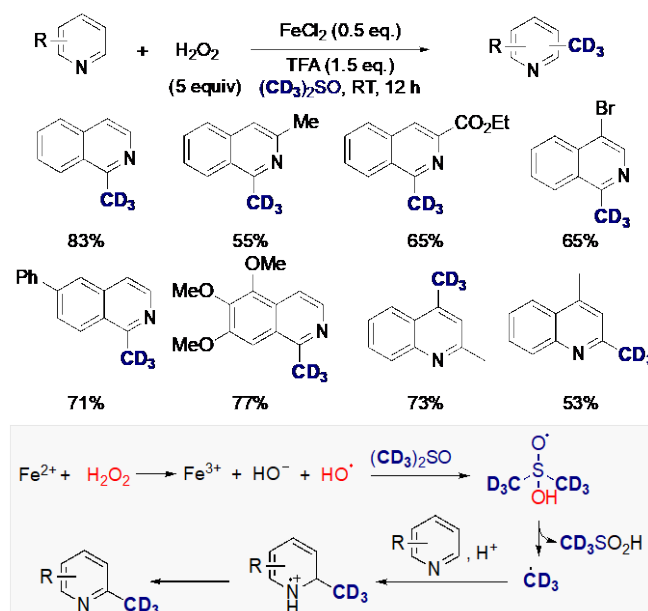


Scheme 37. Pd-catalyzed intermolecular competitive C(sp)–H methylation and trideuteromethylation of terminal alkynes and proposed mechanism

1.7. Radical Reactions

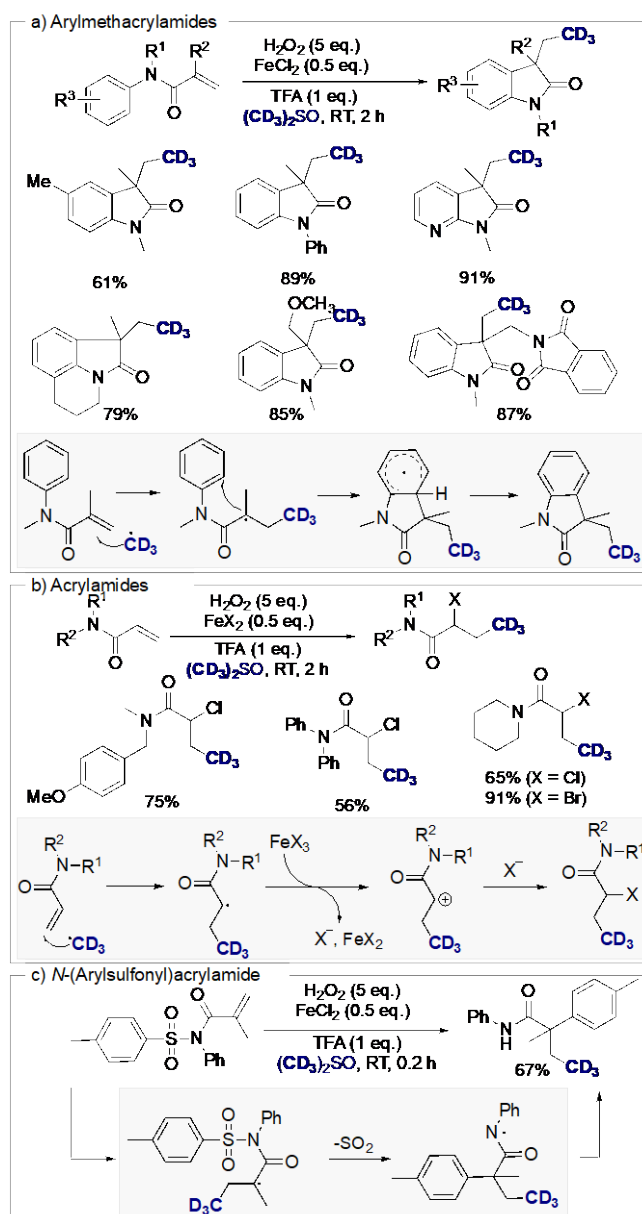
Radical-based C–H functionalization and cascade reactions are convenient methods for elaborating aromatic heterocycles.⁷⁷⁻⁷⁹ In most cases, the reaction is triggered by the generation of radicals –•CD₃ in this case– using either a stoichiometric amount of oxidants coupled with metal salts or, more recently, 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 *d*₆-DMSO as a CD₃ radical source (Scheme 38).⁸⁰ 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 *d*₆-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.



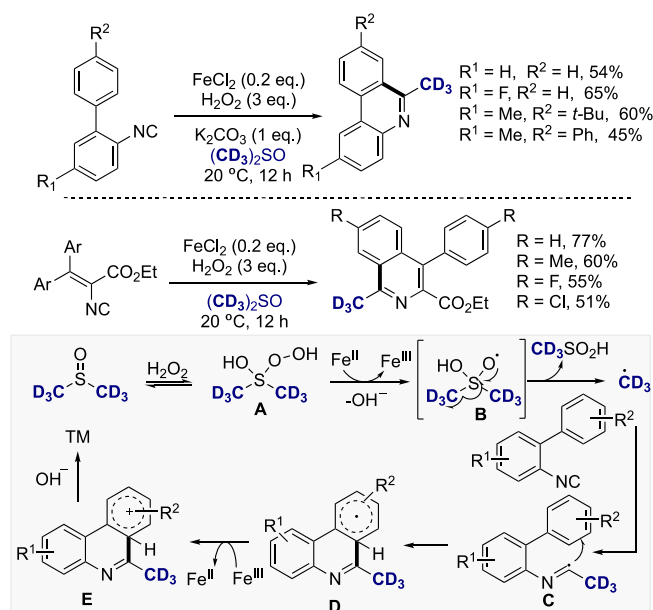
Scheme 38. Radical trideuteromethylation of (iso)quinolines with *d*₆-DMSO

They also extended this CD₃ radical chemistry to cascade trideuteromethylation of a set of acrylamides, including *N*-arylmethacrylamides, acrylamides, and *N*-(arylsulfonyl)acrylamide (Scheme 39)⁸⁰ 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.



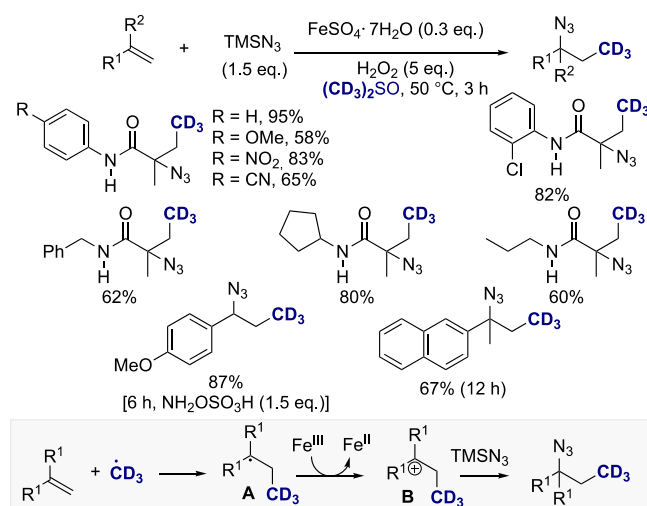
Scheme 39. Radical trideuteromethylation of various acrylamides with d_6 -DMSO

Qi and Li have also used d_6 -DMSO to synthesize trideuteromethylated phenanthridines and isoquinolines *via* CD_3 radical-initiated cascade trideuteromethylation/cyclization of aryl or vinyl isocyanides under Fenton conditions (Scheme 40).⁸¹ The authors proposed a similar generation of $\cdot CD_3$ promoted by $Fe(II)/H_2O_2$, 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_2CO_3 was added in some reactions to counteract the influence of the acid by-product on the reaction yield.



Scheme 40. Fe-mediated radical cascade trideuteromethylation of isocyanides with d_6 -DMSO

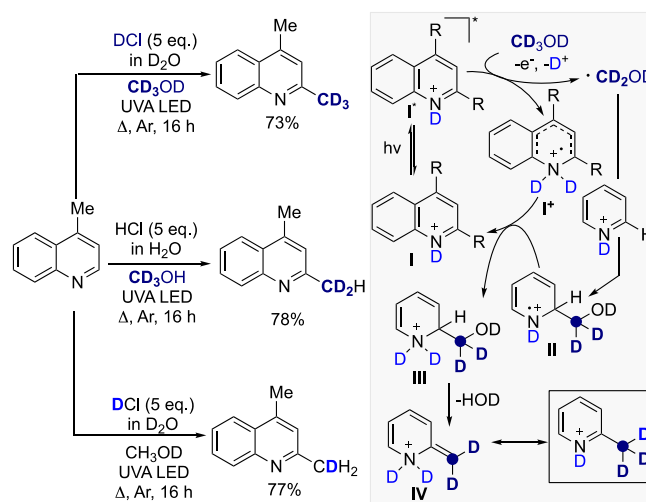
In 2018, Qi and Li reported Fe-mediated radical azidotrideuteromethylation of acrylamides and styrenes under Fenton conditions using TMSN_3 and d_6 -DMSO (Scheme 41).⁸² A series of *N*-aryl, *N*-benzyl, and *N*-alkylacrylamides were difunctionalized in high yields. In the case of styrenes, sometimes $\text{NH}_2\text{OSO}_3\text{H}$ should be added to facilitate the azidotrideuteromethylation. CD_3 radical is firstly generated from d_6 -DMSO with $\text{Fe}(\text{II})/\text{H}_2\text{O}_2$. Once the CD_3 radical addition into alkenes, the carbon-centered radical **A** is oxidized by $\text{Fe}(\text{III})$. Finally, the cation **B** is trapped by TMSN_3 .



Scheme 41. Azidotrideuteromethylation of acrylamides and styrenes with TMSN_3/d_6 -DMSO and proposed mechanism

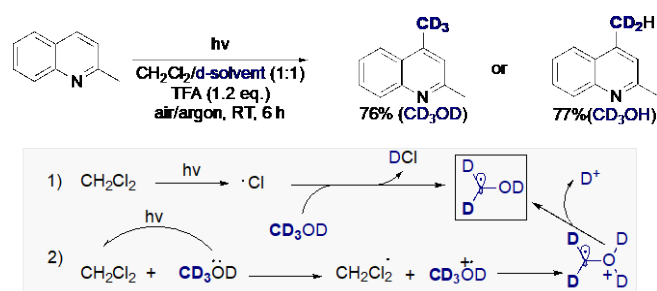
In 2017, the Barriaut group and Scaiano group collaboratively developed photo-mediated (UVA) methylation of pyridines, quinolines, and phenanthridines using methanol as both the solvent and the methylating reagent in the presence of hydrochloric acid (Scheme 42).⁸³ Selective formations of CD_3 , CD_2H , and CDH_2 products could be achieved using a combination of $\text{CD}_3\text{OD}/\text{DCl}$, $\text{CD}_3\text{OH}/\text{HCl}$, or $\text{CH}_3\text{OD}/\text{DCl}$, 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

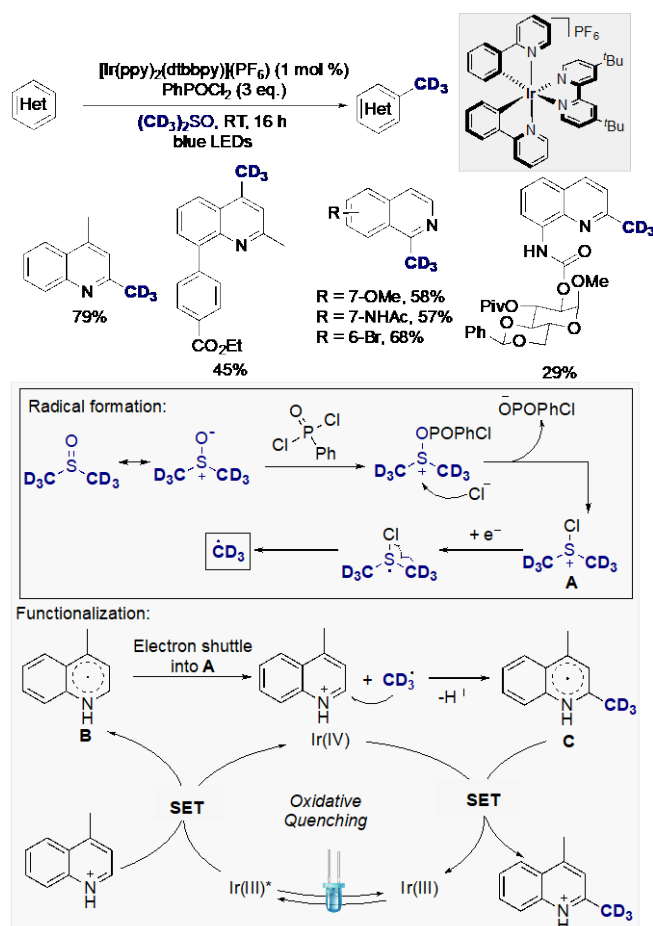
In 2017, similar work was developed by Li and co-workers, albeit they use CH₂Cl₂ as co-solvent to facilitate the generation of the hydroxymethyl radical and trifluoroacetic acid to protonate the heteroarene (Scheme 43).⁸⁴ Using CD₃OD as the solvent, trideuteromethylation of 2-methylquinoline was achieved in 76% yield. Deuterium-labeling experiment of 2-methylquinoline with *d*₃-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

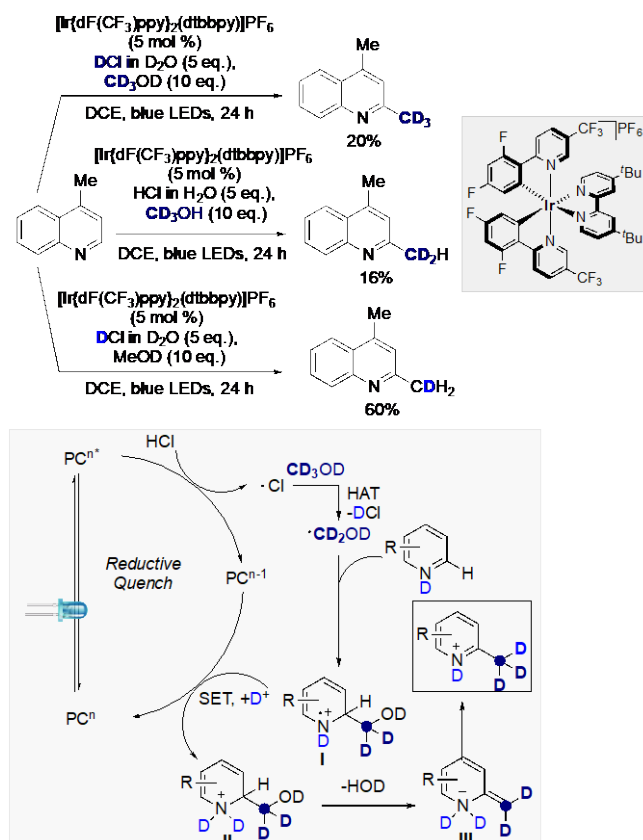
In 2018, Glorius and co-workers employed *d*₆-DMSO as CD₃ radical precursor in Ir-photoredox-catalyzed C–H trideuteromethylation of heteroarenes using PhPOCl₂ as the activator under visible light irradiation (Scheme 44).⁸⁵ A series of quinolines and isoquinolines were successfully trideuteromethylated 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(trideuteriomethyl)sulfonium **A**, which is produced from *d*₆-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.



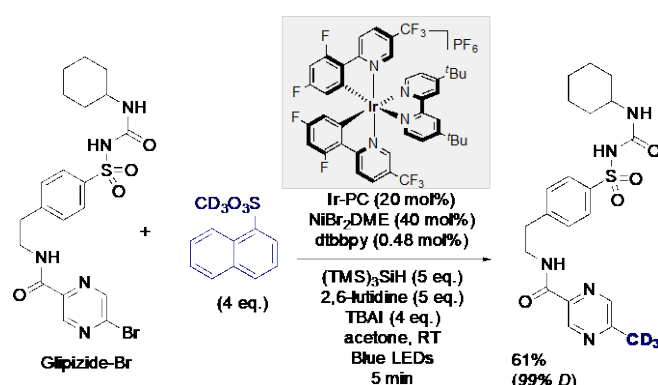
Scheme 44. Ir-photoredox-catalyzed trideuteromethylation of heteroarenes with *d*₆-DMSO

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 $\text{CD}_3\text{OD}/\text{DCl}$, $\text{CD}_3\text{OH}/\text{HCl}$, or $\text{CH}_3\text{OD}/\text{DCl}$ and the proposed mechanism

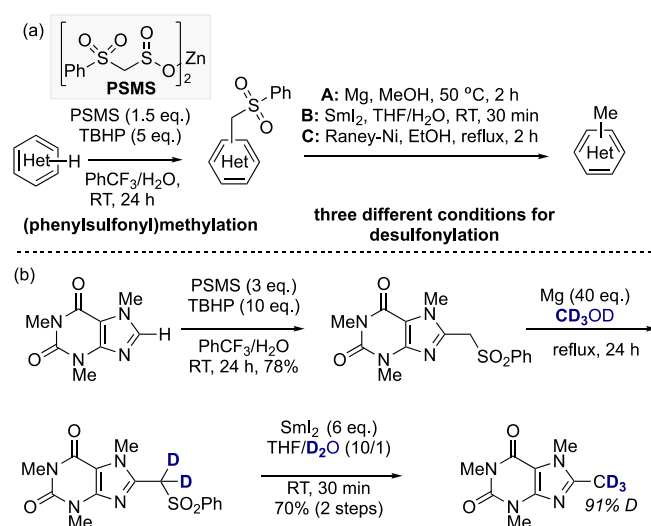
In 2021, during their investigation on the preparation of positron emission tomography radioligands through photoredox-catalyzed tritium (CT_3) and carbon-11 ($^{11}\text{CH}_3$)-labeled methylation, MacMillan and co-workers have also reported the trideuteromethylation of Glipizide-Br (Scheme 46).⁸⁷ 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).⁸⁸ The

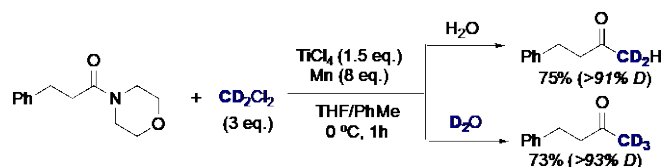
reaction proceeds *via* a two-step process involving TBHP-mediated (phenylsulfonyl)methylation with PSMS followed by Mg/MeOH, SmI₂/H₂O/THF, or Raney-Ni/EtOH mediated desulfonylation to reveal the methyl group. As exemplified by the three-step synthesis of trideuteromethylcaffeine from caffeine, the indirect methylation protocol could be extended to trideuteromethylation *via* sequential dideuteration and desulfonyldeuteration of the (phenylsulfonyl)methylated intermediate by stepwise treatment with Mg/CD₃OD and SmI₂/D₂O. 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

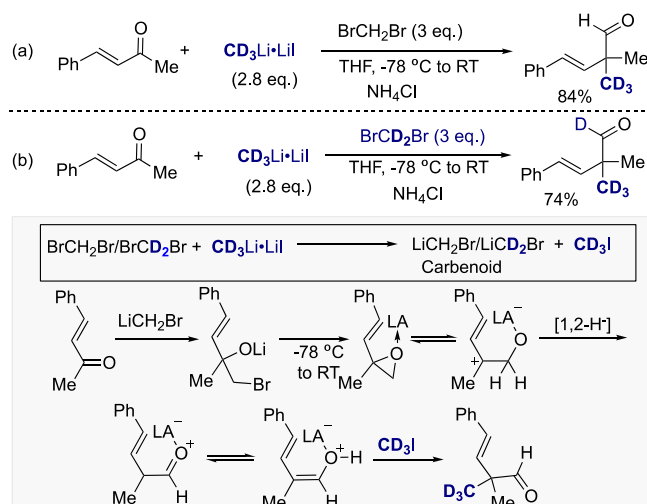
1.8. Other Transformations

In 2008, Yan and co-workers prepared α -dideuteromethyl ketones and α -trideuteromethyl ketones through TiCl₄/Mg-promoted carbonyl-methylenation of amides with CD₂Cl₂ followed by hydrolysis of the resulting enamines with H₂O or D₂O (Scheme 48).⁸⁹



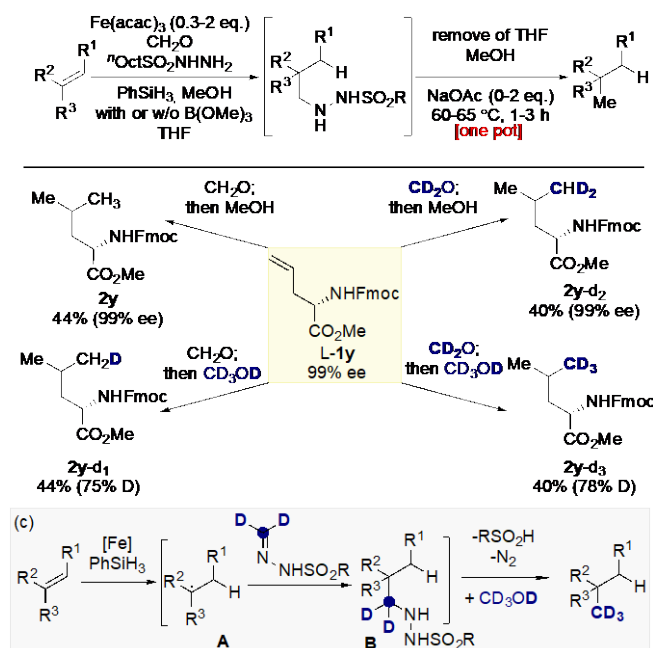
Scheme 48. Ti-Mg promoted synthesis of methyl and deuterated methyl ketones *via* coupling of amides with CH₂Cl₂/CD₂Cl₂

In 2017, Pace and co-workers achieved the synthesis of α -CD₃-substituted β,γ -unsaturated aldehydes from α,β -unsaturated ketones using a lithium carbenoid precursor CH₂Br₂/CD₂Br₂ and CD₃Li•LiI (Scheme 49).^{90, 91} The combination of CH₂Br₂/CD₂Br₂ with CD₃Li•LiI firstly gives the carbenoid LiCH₂Br/LiCD₂Br together with CD₃I. LiCH₂Br/LiCD₂Br-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 CD₃I leads to the desired α -CD₃-substituted β,γ -unsaturated aldehydes. It should be noted that deuteration at both the aldehyde and its α -position was achieved for the D₂-carbenoid precursor. On the other hand, only α -trideuteromethylation was observed for the H₂-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, *n*OctSO₂NHNH₂, and MeOH (Scheme 50).⁹² 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 hydrazide **B**. Then reductive C–N bond cleavage of the alkyl hydrazide in the presence of CD₃OD produces the hydrotrideuteromethylation product.



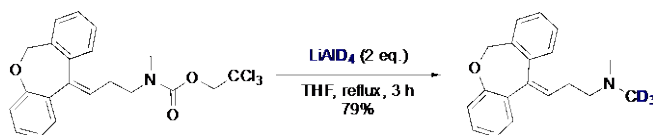
Scheme 50. Hydromethylation/deuterated hydromethylation of unactivated olefins and proposed mechanism

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}

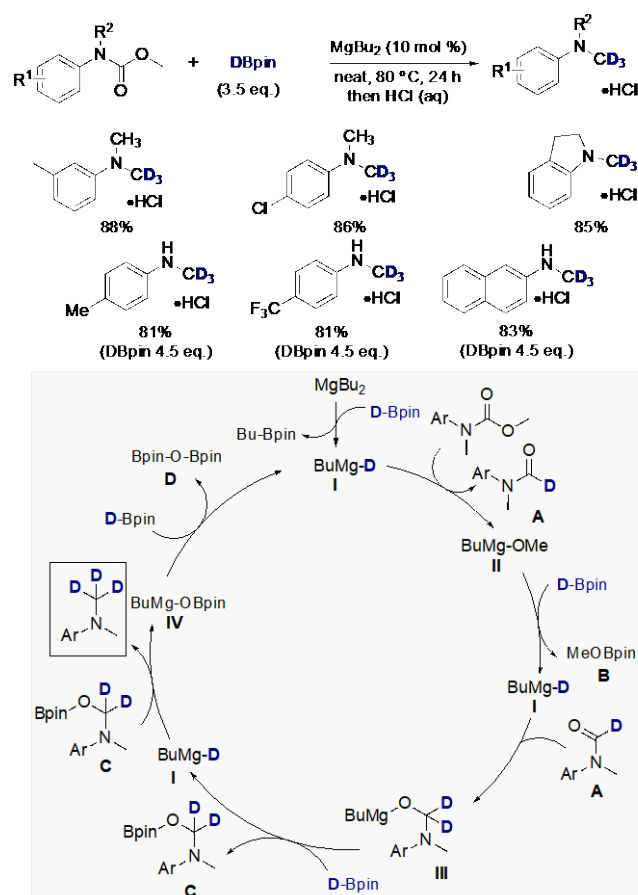
2.1. Functional Group Conversion

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.



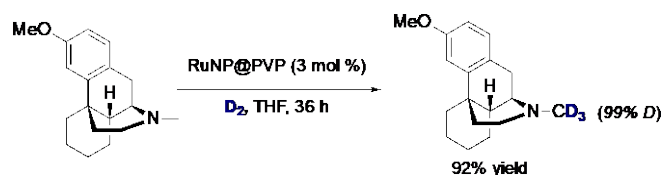
Scheme 51. LiAlD₄-mediated reduction of *N*-carbamate

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**.



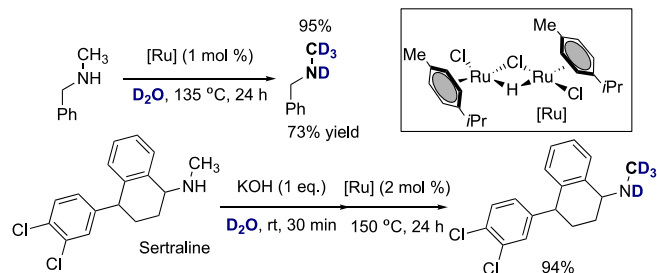
Scheme 52. MgBu_2 -catalyzed reduction of carbamates with DBpin

Besides the reduction of carbamates, the N-CD_3 group can be generated through H/D exchange using metal nanoparticles in the presence of D_2 . In 2014, Rousseau and Chaudret selectively incorporated three deuterium atoms at the $N\text{-Me}$ group of dextromethorphan using Ru nanoparticles stabilized on PVP (PVP = polyvinylpyrrolidone) (Scheme 53).⁹⁷ The deuteration took place regioselectively at the $N\text{-Me}$ group since other C–H bonds at the α -position of nitrogen are embedded in the six-membered ring and are thus less accessible.



Scheme 53. Ru@PVP nanoparticles-catalyzed H-D exchanges of dextromethorphan

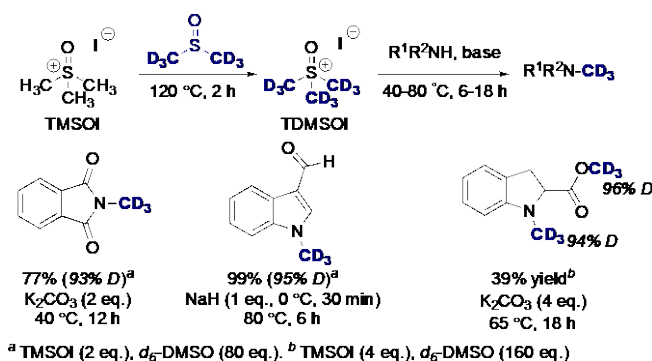
In 2016, Gunanathan and co-workers reported α -selective deuteration of amines and amino acids with D_2O using monohydrido-bridged dinuclear ruthenium complex.⁹⁸ For N -methyl substituted substrates such as N -methyl- N -benzylamine and sertraline, the deuteration selectively occurred at the N -methyl groups (Scheme 54).



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

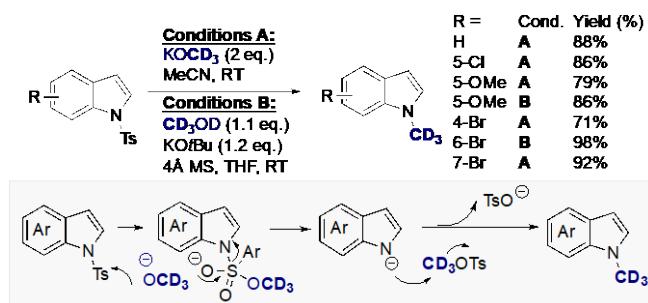
2.2. *N*-Trideuteromethylation of Amines and Derivatives

Traditionally, *N*-methyl amines are prepared by reactions of primary or secondary amines with S_N2 -methylating agents. The *N*-methylation of primary amines is usually hampered by over methylation. Amid the previously developed TMSOI reagent is also employed for the *N*-trideuteromethylation of phthalimide, indole, and indoline (Scheme 55).⁴⁵ Notably, simultaneous *N*- and *O*-trideuteromethylation was observed when indoline-2-carboxylic acid was the substrate.



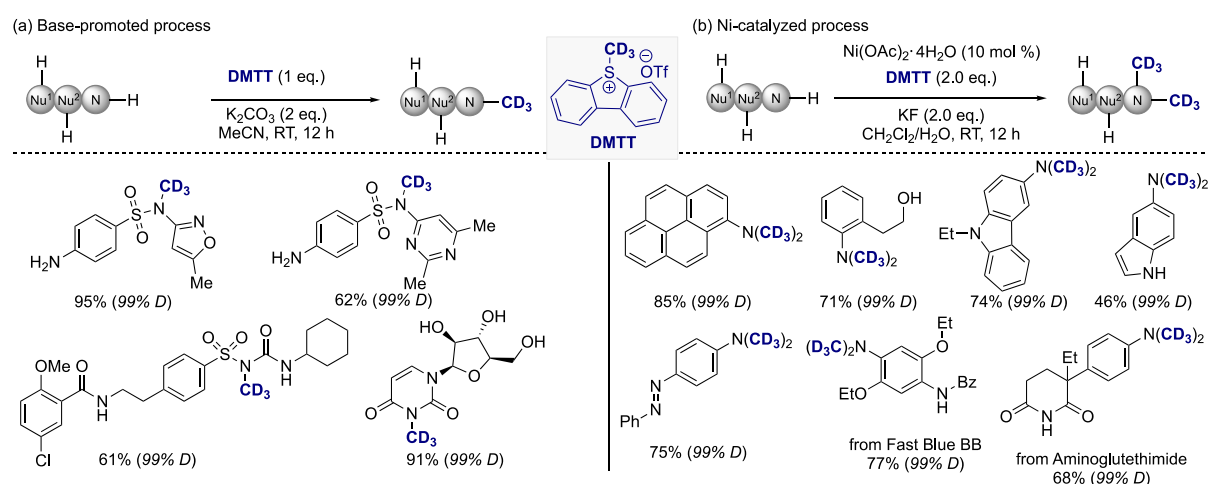
Scheme 55. *N*-trideuteromethylation of acidic amines with TMSOI

In 2019, Liu and co-workers reported the *in-situ* generation of CD_3OTs in *ipso*-detosylative *N*-trideuteromethylation of *N*-tosylindoles using $KOCD_3$ (Scheme 56).⁹⁹ CD_3OTs is generated from the nucleophilic attack of CD_3O^- on the sulfonamide, followed by the cleavage of the indole *N*-S bond. A subsequent S_N2 attack of the *N* anion on CD_3OTs affords the *N*-trideuteromethylation product. Alternatively, $KOCD_3$ was also *in-situ* generated from KO^tBu and CD_3OD .



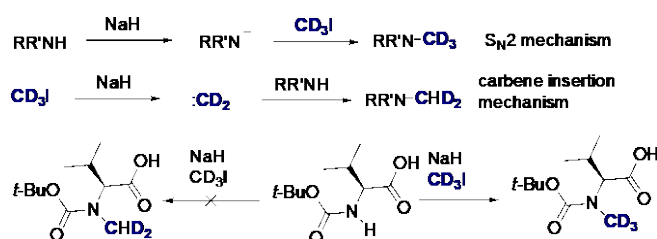
Scheme 56. Detosylative *N*-trideuteromethylation of indoles with $KOCD_3$ and reaction mechanism

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).⁷¹ 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).¹⁰⁰ An isotopic labeling experiment with CD₃I affords the *N*-CD₃ product instead of the *N*-CHD₂ product, suggesting that the methylation proceeds *via* a S_N2 mechanism instead of an alternative mechanism involving the formation of the carbene intermediate :CD₂ and its insertion into the N–H bond.

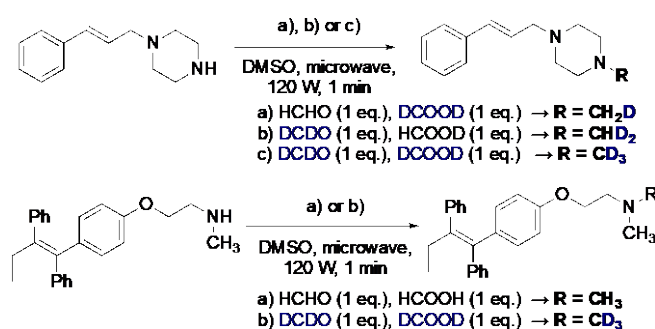


Scheme 58. Mechanistic elucidation of *N*-trideuteromethylation with CD₃I

2.3. Reductive Amination

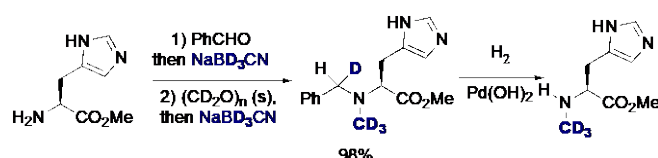
Besides electrophilic methylation with CD₃ reagents, *N*-trideuteromethylation could also be achieved *via* reductive amination with formaldehyde or formaldehyde equivalent in the presence of a reducing reagent such as formic acid and metal hydrides. In 2002, a microwave-assisted Eschweiler-Clarke methylation of amines was reported by Jones and co-workers using formic acid-formaldehyde mixtures as the methyl donor (Scheme 59).¹⁰¹ Since the newly introduced methyl group is derived from one carbon and two hydrogen atoms of HCHO and one hydrogen of HCOOH, selective *N*-monodeuterio-, *N*-dideuterio- and *N*-trideuteromethylation of *trans*-cinnamyl piperazine were achieved using combination of HCHO/DCOOD, DCDO/HCOOH or

DCDO/DCOOD, respectively. Furthermore, the reaction also allows for the synthesis of the antineoplastic drug Tamoxifen and its CD₃ analog.



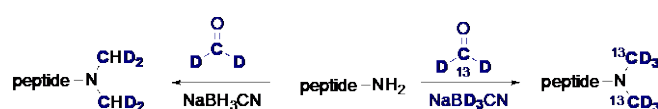
Scheme 59. Microwave-assisted methylation and deuteriomethylation of amines using the appropriately deuterated HCOOH-HCHO mixture

In 2005, Konopelski and co-workers reported the preparation of *N*-CD₃-labeled histidine methyl ester *via* sequential reductive 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.



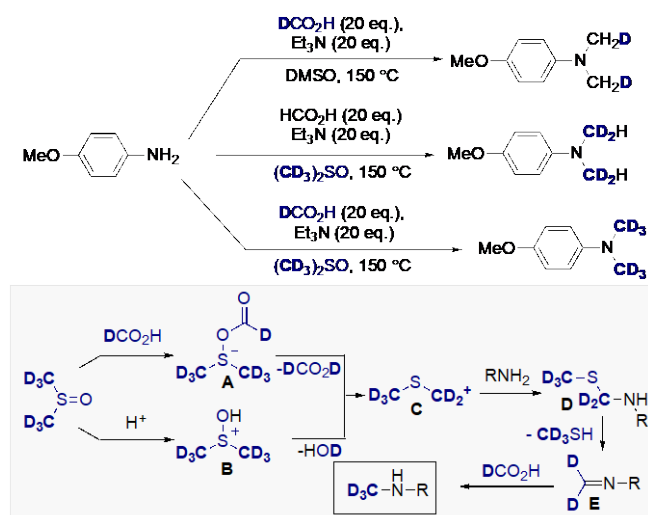
Scheme 60. Reductive amination with (CD₂O)_n and NaBD₃CN

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}



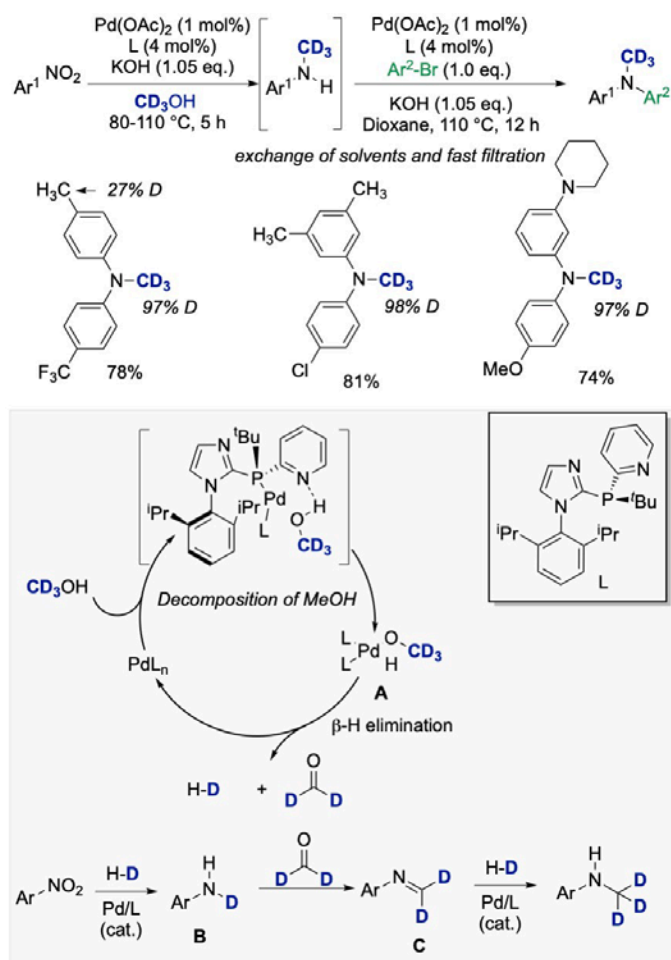
Scheme 61. Preparation of stable-isotope dimethyl labeled peptides

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, *d*₆-DMSO/HCO₂H, and *d*₆-DMSO/DCO₂H, respectively. As for the trideuteromethylation, the reaction of *d*₆-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.



Scheme 62. Selective *N*-deuteromethylation of amines with DMSO/DCO₂H, *d*₆-DMSO/HCO₂H, or *d*₆-DMSO/DCO₂H and proposed mechanism

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 CD₃OH 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 CD₃OD. 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 CD₃OH to the nitrogen of the pyridyl group of the ligand. O–H cleavage of CD₃OH by coordinated palladium followed by β-D elimination of the resulting CD₃O–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 CD₂O produces a deuterated imine intermediate **C** which undergoes Pd-catalyzed hydrogenation to afford the final *N*-CD₃-arylamines.



Scheme 63. Pd-catalyzed reductive *N*-trideuteromethylation of nitroarenes with CD₃OH

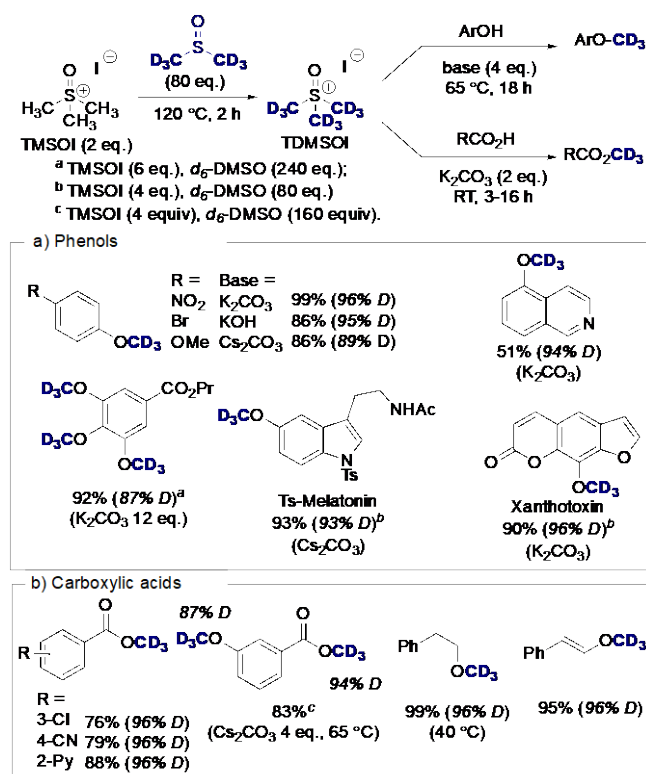
3. Organic Molecules Containing O–CD₃ Bond

The ether linkage is the single most common and unifying structural feature, generally prepared by S_N2 reaction between alkoxides of phenoxides with alkyl halides, so-called Williamson ether synthesis. Trideutomethyl ethers can be prepared either by forming O–CD₃ bond using electrophilic CD₃ reagents or C–OCD₃ bond formation *via* trideuteromethoxylation. This latter case is mostly employed for the construction of deuterated anisole derivatives. Trideuteromethyl esters are another class of molecules containing the O–CD₃ bond. They are generally prepared from corresponding carboxylic acids.

3.1. *O*-Trideuteromethylation of Phenol Derivatives and Carboxylic Acids

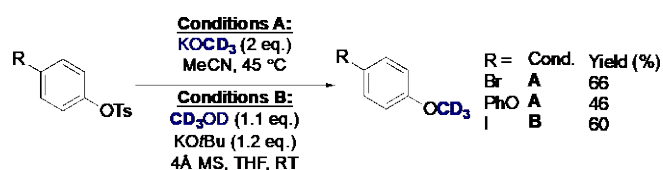
Classical approaches to *O*-trideuteromethylation generally involve nucleophilic attack of *O*-nucleophiles with electrophilic CD₃ reagents under strongly basic conditions¹⁰⁸⁻¹¹¹ or acidic conditions.¹¹² Due to the toxicity associated with the commonly used electrophilic CD₃ reagents such as CD₃I, (CD₃)₂SO₄, 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.



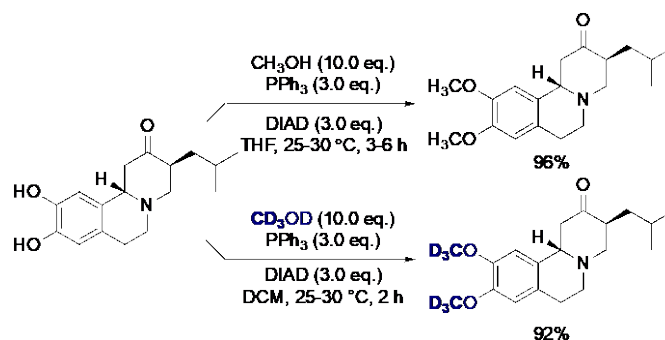
Scheme 64. *O*-trideuteromethylation of phenols and carboxylic acids with TDMSOI

In the previous section, we have discussed KOCD₃ as the CD₃ 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 KOCD₃ as the trideuteromethylating reagent (Scheme 65).⁹⁹



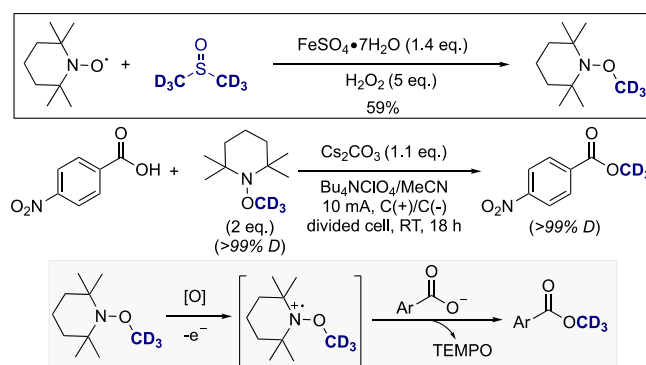
Scheme 65. Detosylative *O*-trideuteromethylation of *O*-tosylphenols

In 2018, Ray and co-workers developed a novel, cheap and industrially scalable process for the synthesis of tetrabenazine and deutetetrabenazine, *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 CD₃OD using the classical Mitsunobu reaction in the presence of PPh₃ and DIAD. Unlike previous reported methods using genotoxic CH₃I and CD₃I, the novel process for the synthesis of tetrabenazine and deutetetrabenazine is relatively safe.



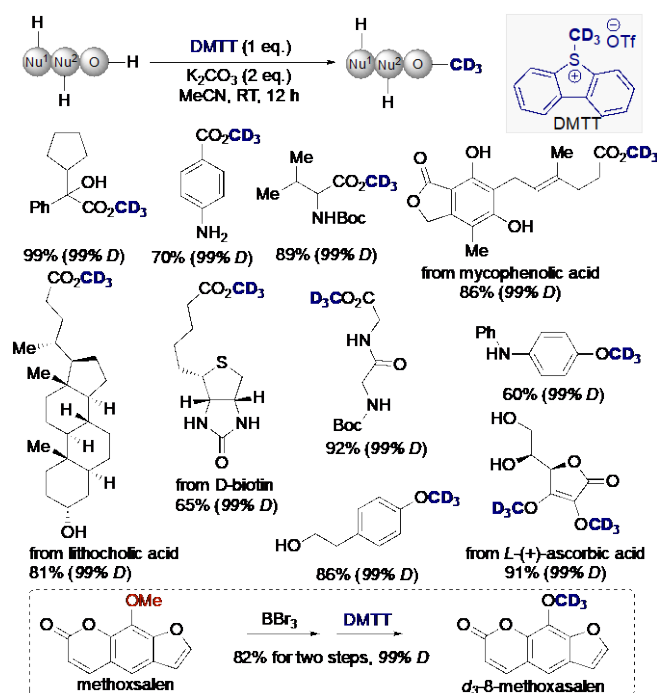
Scheme 66. Synthesis of tetrabenazine and deutetetrabenazine via Mitsunobu reaction with CH_3OH or CD_3OD

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).¹¹⁴ 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 $\text{S}_{\text{N}}2$ 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

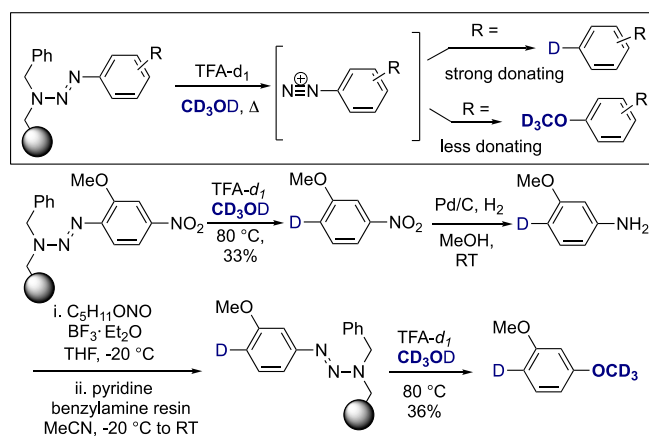
As described for *N*-trideuteromethylation, DMTT could also mediate selective *O*-trideuteromethylation of carboxylic acids and phenols in the presence of other functional groups such as alcohol hydroxyl, amino, and amide groups (Scheme 68).⁷¹ The reactivity of carboxylic acids is better than that of 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.



Scheme 68. *O*-trideuteromethylation of carboxylic acids and phenols with DMTT

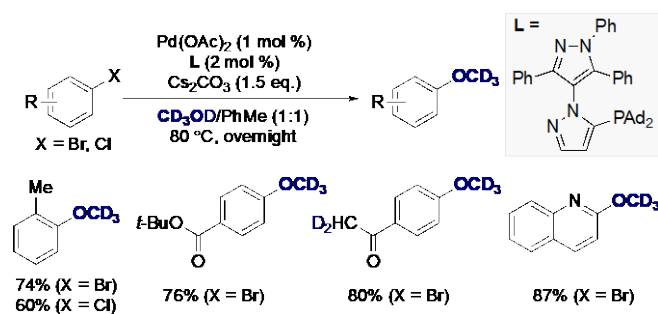
3.2. C(sp²)-Trideuteromethoxylation

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-dediazotiation using CD₃OD as the deuterium source (Scheme 69).¹¹⁵ 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.



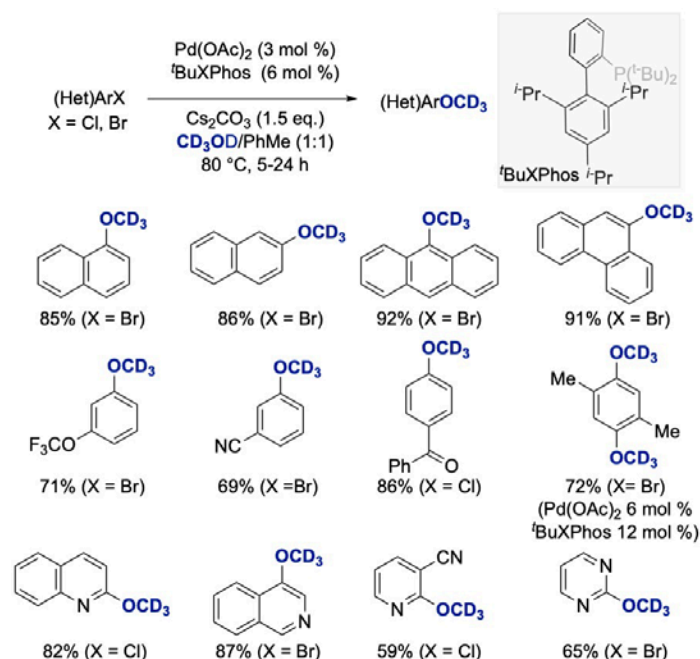
Scheme 69. Generation of monodeuterated and D₃CO-substituted arenes from triazene resins in CD₃OD

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 bispyrazolyphosphine as ligand (Scheme 70).¹¹⁶ 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.²⁵



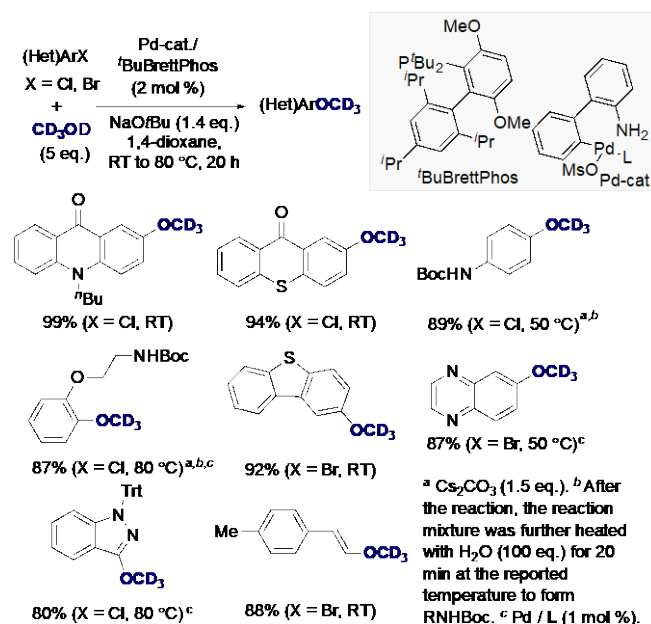
Scheme 70. Pd-catalyzed trideuteromethoxylation of (hetero)aryl halides with CD_3OD

In the same year, Peruncheralathan and co-workers also described a similar Pd-catalyzed trideuteromethoxylation of (hetero)aryl halides with CD_3OD , albeit they employed *t*BuXPhos as commercially available ligand (Scheme 71).¹¹⁷ The sterically bulky diaryl phosphine ligand also reduces the competing β -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.



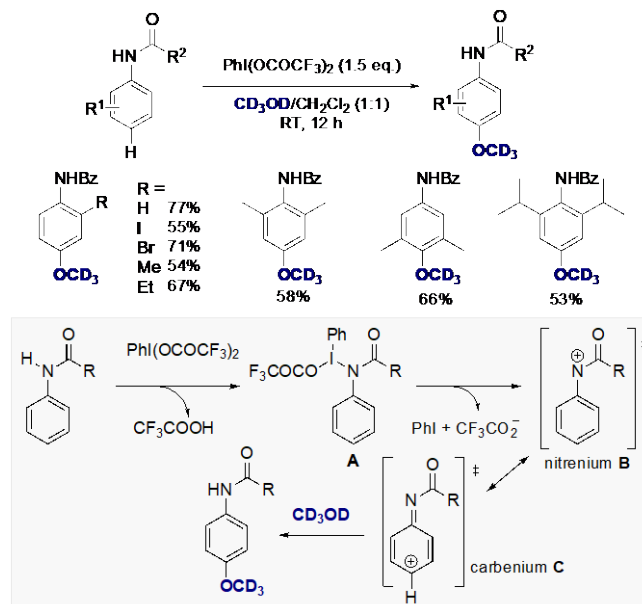
Scheme 71. Pd-catalyzed trideuteromethoxylation of (hetero)aryl halides

In 2013, Buchwald and co-workers developed a room temperature Pd-catalyzed coupling of (hetero)aryl halides with 5 equivalents of CD_3OD (Scheme 72).^{118, 119} 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 72. Pd-catalyzed arylation or vinylation of CD_3OD

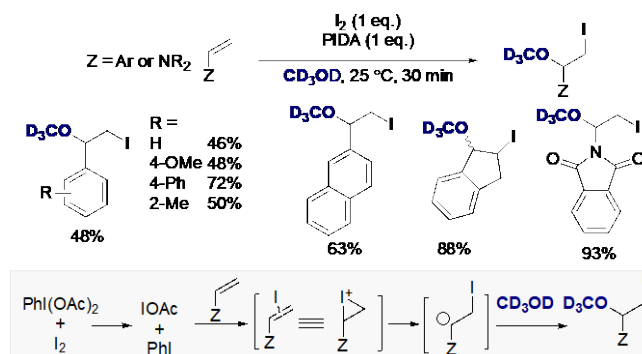
In 2018, Mai and co-workers developed a mild, metal-free *para*-C–H trideuteromethoxylation of anilides *via* PIFA-mediated soft-hard acid-base (SHAB)-controlled cross dehydrogenative coupling with CD_3OD (Scheme 73).¹²⁰ Both electron-withdrawing and electron-donating anilides were suitable partners. 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_3COO^- to give the nitrenium ion **B**, which could resonate to the harder carbenium ion **C**. Finally, a nucleophilic attack of CD_3OD delivers the OCD_3 -incorporating aryl ethers.



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

In addition to the above discussed $\text{C}(\text{sp}^2)$ -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-I₂ mediated vicinal iodotrideuteromethoxylation of alkenes using CD₃OD as the nucleophilic solvent (Scheme 74).¹²¹ 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 I₂ 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 CD₃OD on this cationic intermediate delivers the final product.



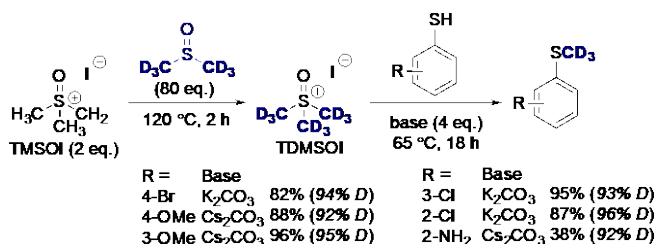
Scheme 74. PIDA-I₂ mediated iodotrideuteromethoxylation of alkenes with CD₃OD

4. Organic Molecules Containing S-CD₃ 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-CD₃ bond is therefore important for biological application but also for mechanism understanding. Like ether bonds, the thioether bonds can be generated by either S-CD₃ or C-SCD₃ bond formations. However, compared with C/N/O-trideuteromethylation, the examples of S-trideuteromethylation are relatively few.

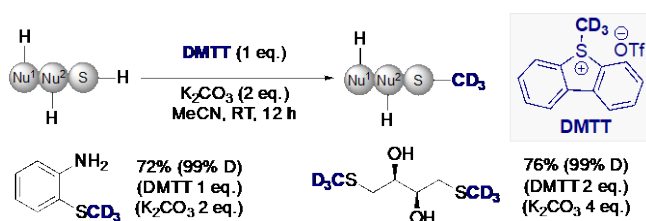
4.1. S-Trideuteromethylation of Thiophenol Derivatives

In 2019, Wang and Chen successfully prepared a range of trideuteromethyl aryl thioethers *via* S-trideuteromethylation of the corresponding thiophenols with TDMSOI (Scheme 75).⁴⁵ 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

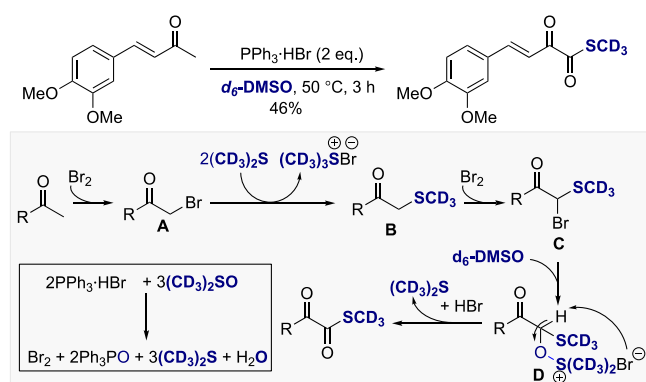
Besides the above-mentioned *N*- and *O*-trideuteromethylation, DMTT was also used for selective *S*-trideuteromethylation of thiophenols and mercapto-bearing compounds (Scheme 76).⁷¹ Amine and hydroxyl groups remained intact in these reactions.



Scheme 76. *S*-trideuteromethylation with DMTT

4.2. Formation of C–SCD₃ bond

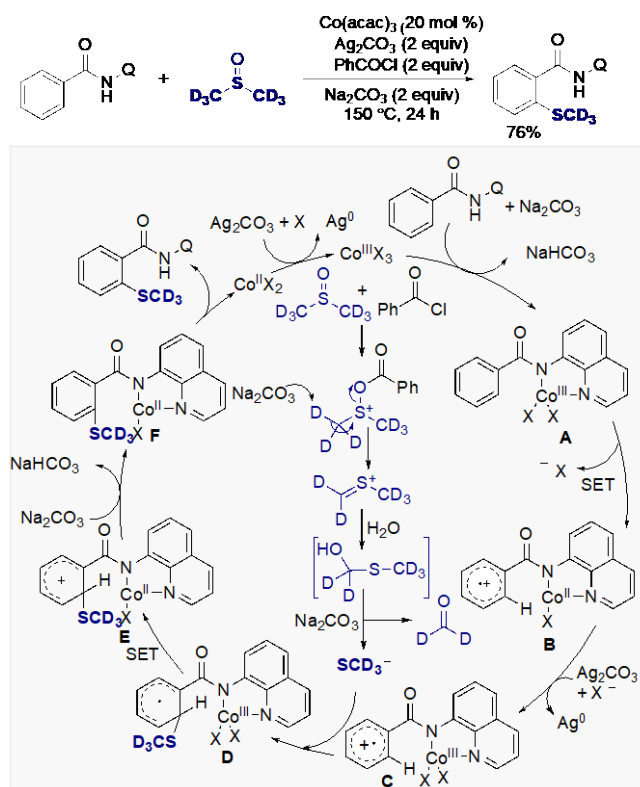
DMSO often serves as a methyl source, but it can also be a source of methylthiol in organic synthesis.¹²² In 2014, Das and co-workers reported the synthesis of γ -substituted β,γ -unsaturated α -ketomethylthioesters from α,β -unsaturated ketomethyl derivatives *via* PPh₃•HBr-DMSO-mediated methylthioesterification (Scheme 77).¹²³ When *d*₆-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 *d*₆-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 *d*₆-DMSO-mediated Kornblum oxidation delivers the final trideuteromethylthioesterification product.



Scheme 77. Trideuteromethylthioesterification with PPh₃•HBr/*d*₆-DMSO and the proposed mechanism

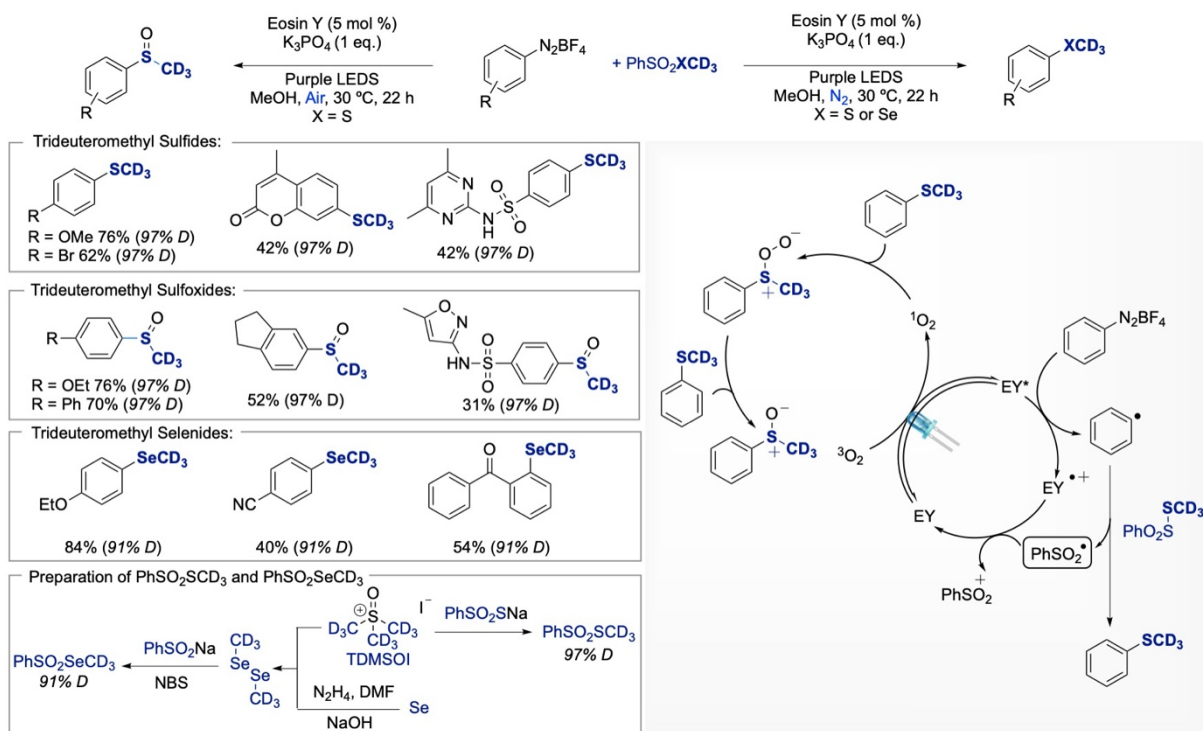
In 2018, Gui and Tan described cobalt-catalyzed, 8-AQ directed highly mono-selective *ortho*-methylthiolation of benzamides and acrylamides using DMSO as the methylthiolating reagent and PhCOCl as the additive, respectively (Scheme 78).¹²⁴ Using *d*₆-DMSO as the -SCD₃ source, C–H trideuteromethylthiolation of the 8-AQ bearing benzamide was achieved in 76% yield. The reaction starts with the complexation of Co^{III}X₃ 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 *d*₆-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 $\text{Co}^{\text{II}}\text{X}_2$ regenerates the catalytically active Co^{III} species and closes the catalytic cycle.



Scheme 78. Co-catalyzed *ortho*-trideuteromethylthiolation of substituted benzamide with d_6 -DMSO

In 2020, Wang and coworkers reported a visible-light-promoted trideuteromethylthiolation/trideuteromethylselenation of aryldiazonium salts using $\text{PhSO}_2\text{SCD}_3$ or $\text{PhSO}_2\text{SeCD}_3$ as the novel deuterated methylation reagents using Eosin Y as photosensitizer (Scheme 1).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.¹²⁶ Mechanistically, upon visible-light irradiation of EY gives EY^* , SET transfer event with the aromatic diazonium salt generates $\text{EY}^{+\bullet}$ and an aryl radical. The latter reacts with $\text{PhSO}_2\text{SCD}_3$ to afford the (methyl- d_3)thiolation product together with a sulfone radical. A second SET transfer between $\text{EY}^{+\bullet}$ and the sulfone radical regenerates EY to complete the catalytic cycle. In the presence of air, further oxidation of the (methyl- d_3)methylthiolation product with $^1\text{O}_2$, which is generated via energy transfer between $^3\text{O}_2$ 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 CD₃-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 D₂ as safer deuteride sources and the development of catalytic hydrogen borrowing strategies, which employed deuterated solvent such as CD₃OD as deuteride surrogate. Such progress has also enabled to build up *N*-CD₃ units by reductive amination from deuterated solvents.

The coupling with nucleophilic trideuteromethyl sources is restrained to C–CD₃ bond formation and suffered from the low diversity of metallic trideuteromethyl reagents. However, the promising recent success of stable CD₃B(OH)₂ combined with the popularity of Suzuki-Miyaura cross-coupling reactions has led to considerable development of more efficient catalytic systems to introduce CD₃ group. On the other way, the coupling with electrophilic trideuteromethyl sources is an excellent solution to link CD₃ 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 CD₃-I, albeit it is a hazardous reagent. Therefore, a new research trend appeared to find safer and easy-to-handle surrogates, such as CD₃-OTs, OP(OCD₃)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–CD₃, 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 CD₃ 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 paved 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, trideuteromethylation 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 *O*CD₃ and *S*CD₃ 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”.

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Bibliography



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