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# Spontaneous conversion of prenyl halides to acids: application in metal-free preparation of deuterated compounds under mild conditions†

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Here we reveal a simple generation of deuterium halide (DX) from common and inexpensive reagents readily available in a synthetic chemistry laboratory, *i.e.* prenyl-, allyl-, and propargyl halides, under mild conditions. We envisaged that *in situ* generation of an acid, deuterium halide, would be useful for acid-catalyzed reactions and could be employed for organocatalytic deuteration. The present work reports a metal-free method for deuterium labeling covering a broad range of substrate including phenolic compounds (*i.e.* flavonoids and stilbenes), indoles, pyrroles, carbonyl compounds, and steroids. This method was also applied for commonly used drugs such as loxoprofen, haloperidol, stanolone, progesterone, androstenedione, donepezil, ketorolac, adrenosterone, cortisone, pregnenolone, and dexamethasone. A gram-scale chromatography-free synthesis of some deuterated compounds is demonstrated in this work. This work provides a simple, clean and by-product-free, site-selective deuteration, and the deuterated products are obtained without chromatographic separation. When applying these initiators for other acid-catalyzed reactions, the deuterium isotope effects of DX may provide products which are different from those obtained from reactions using common acids. Although the mechanism of the spontaneous transformation of prenyl halides to acid is unclear, this overlooked chemistry may be useful for many reactions.

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## Introduction

Prenyl halides are common reagents in organic synthesis and are widely used for many reactions. The spontaneous transformation of prenyl halides to acids, hydrogen halides (HX) or deuterium halides (DX), is observed when these reagents are dissolved in alcohol. The generation of DX from prenyl bromide (3,3-dimethylallyl bromide) (**1**), prenyl chloride (**2**), allyl bromide (**3**), and propargyl bromide (**4**) under mild conditions in $CD_3OD$ was observed (Fig. 1) and it was useful for acid-catalyzed reactions. In the present work, we demonstrate the *in situ* generation of DX for acid-catalyzed deuteration reactions.

Isotopic labelling of organic compounds with deuterium is of great interest in the fields of organic synthesis and the pharmaceutical industry,[1–3] and recently a number of efficient methods for the deuteration of organic compounds have been developed either by chemical synthesis[4–8] or by biological approaches.[9,10] Deuterated forms of existing drugs can have improved and distinct pharmacokinetic or toxicological properties because of the stability of C–D bonds,[3,11] and there have been a number of patents and clinical trials of deuterated versions of known drugs.[12] Many drug companies have filed a number of patents on drug deuteration, showing improvements in drug pharmacokinetics.[12] On account of the higher stability of the C–D bond relative to the C–H bond, deuterated drug candidates have shown an improvement in pharmacokinetics and metabolic profiles with a profound enhancement of half-lives compared to the molecules with C–H bonds without altering the potency.[12,13] With the first deuterated drug being approved by the US FDA in 2017, deuteration of drug molecules and organic compounds has become an increasingly popular field of research.[14,15] Deuterated compounds are widely used for studies on the elucidation of reaction mechanisms and biosynthetic pathways[3,16–19] and as internal standards for mass spectrometry.[20–23]

Deuteration at C-3 of indoles was previously reported using an organocatalyst flavin,[24] Brønsted acid ($HClO_4$),[25] and metals, Ru or Ag (Fig. 1A),[15,26] while deuterated pyrrole deriva-

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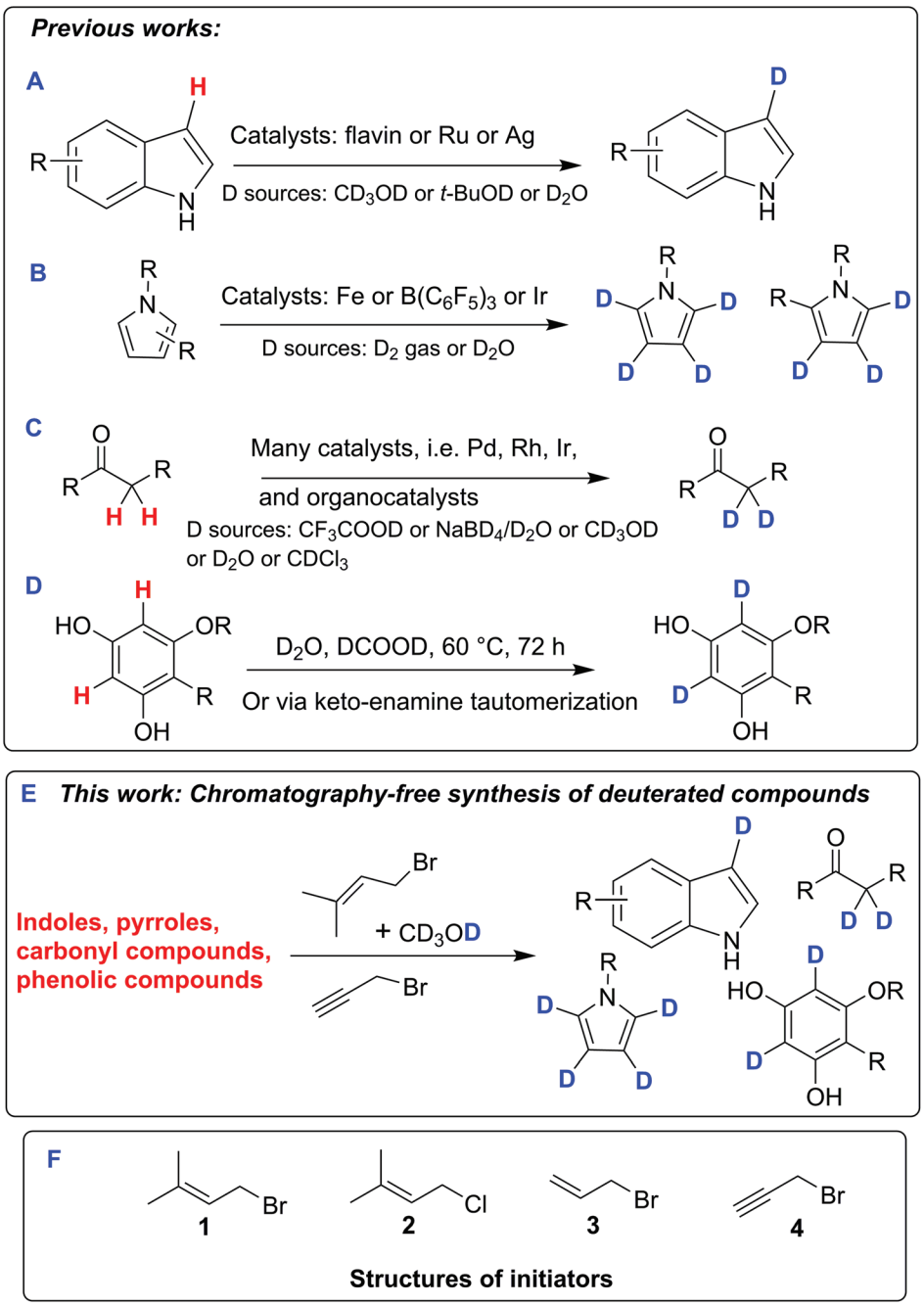



**Fig. 1** Previous works and this work: previous deuteration of (A) indole, (B) pyrrole, (C), carbonyl, and (D) phenolic compounds; the present work; (E) organocatalytic deuteration using prenyl- and propargyl halides, and (F) the structures of initiators **1–4**.

tives (Fig. 1B) were prepared using Fe,[27] Lewis acid $B(C_6F_5)_3$,[28] Brønsted acid ($HClO_4$),[25] and Ir catalysts.[29] A number of works have reported the deuteration of carbonyl compounds using metal catalysts (*i.e.* Pd, Rh, and Ir),[30–33] Lewis acid $B(C_6F_5)_3$,[34] organocatalysts,[35–37] microwave-assisted deuteration,[38] and antibodies (Fig. 1C).[39] Deuteration of phenolic compounds with an aromatic ring which is shown in Fig. 1D was achieved by keto-enamine tautomerization,[40] using a Brønsted acid ($HClO_4$),[25] acid-catalyzed H/D exchange,[41] and microwave irradiation of ionic liquids and $DCl/D_2O$ or with $CF_3COOD$.[42–44] We report herein the generation of deuterium halide from prenyl halides (**1** and **2**), allyl bromide (**3**), and propargyl bromide (**4**) under mild conditions in $CD_3OD$, and we used compounds **1–4** as initiators for the chromatography-free synthesis of deuterated compounds (Fig. 1E). The halogen-containing organic compounds **1–4** have boiling points of 135 °C, 109 °C, 70–71 °C, and 88–90 °C, respectively (Fig. 1F); therefore, they can be removed from the reactions

simply by evaporation under vacuum. Moreover, deuteration by these initiators enables a clean synthesis and has no observable side reactions, and thus no by-products. Therefore, a clean and by-product-free synthesis using initiators **1–4** enables a simple preparation of deuterated compounds, which could be obtained without chromatographic separation. This work reports a repeatable and facile protocol for site-selective deuteration with a broad substrate scope including indole, pyrrole, carbonyl and phenolic compounds as shown in Fig. 1A–D. Moreover, the other merits of this work are the highly selective deuteration of organic compounds and the large scale of the reaction. To our knowledge, this is the first *in situ* acid generation of DBr from organic compounds under mild conditions and may be applied in acid-catalyzed reactions.

## Method

### General procedure for organocatalytic deuteration

A reaction vessel with a glass stopper was charged with a substrate (20–40 mg, 0.1–0.3 mmol), 1 mol% or 3 mol% of initiators **1** or **2**, and $CD_3OD$ (0.6 mL). Note that, in some cases, 10 mol% of an initiator **4** was used for deuteration. The reaction mixture was stirred at room temperature for 16–24 h and then it was evaporated under reduced pressure to remove the initiator and solvent, giving a deuterated compound. The deuteration percentage was determined from the $^1$H NMR spectrum. Details of the experiments can be found in the ESI.†

## Results and discussion

We found that prenyl halides, *i.e.* prenyl bromide (**1**) and prenyl chloride (**2**), in $CD_3OD$ could generate deuterium halide (DX), and this transformation is a spontaneous reaction (Fig. 2). This *in situ* generation of DX occurs at room temperature without any catalysts. Probing the characteristics of prenyl bromide (**1**) in $CD_3OD$ revealed the formation of compounds **5** and **6**, whose structures were identified from NMR data (ESI†). We envisaged that this *in situ* generation of the acid, deuterium halide (DBr or DCl), can be used in acid-catalyzed reactions.

Deuteration could be achieved by acid-catalyzed reactions, for example, using Lewis acidic $B(C_6F_5)_3$ as a catalyst,[28,34] using $H_2SO_4$ in $CD_3OD$ for the deuteration of phenols and phenol ethers[45] and pyrroles,[46] using DCl in $D_2O$ for the deuteration of pyrazoles (at 200–250 °C)[47] and indole ring in tryptamine derivatives,[48] and using $KDSO_4$ and NaOAc in $D_2O$ for the deuteration of simple ketones.[49] To investigate the role of prenyl bromide (**1**) in the deuteration reaction, it was first performed with 3′,5′-dihydroxyacetophenone (**7**) in the presence of $CD_3OD$ as a deuterium source and solvent in the NMR tube. We observed the deuteration (>95%) of aromatic and methyl protons (Scheme 1) when using only 1 mol% or 3 mol% of **1** in $CD_3OD$. It was found that prenyl halides **1** and **2** were the two best substrates for deuteration, followed by allyl bromide (**3**) and propargyl bromide (**4**), respectively. In the deuteration process, halide-containing compounds **1–4** act as the "initiator" of the reaction producing deuterium halide, the deuterating agent in the deuteration reaction.

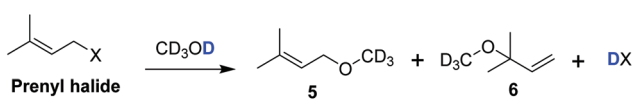
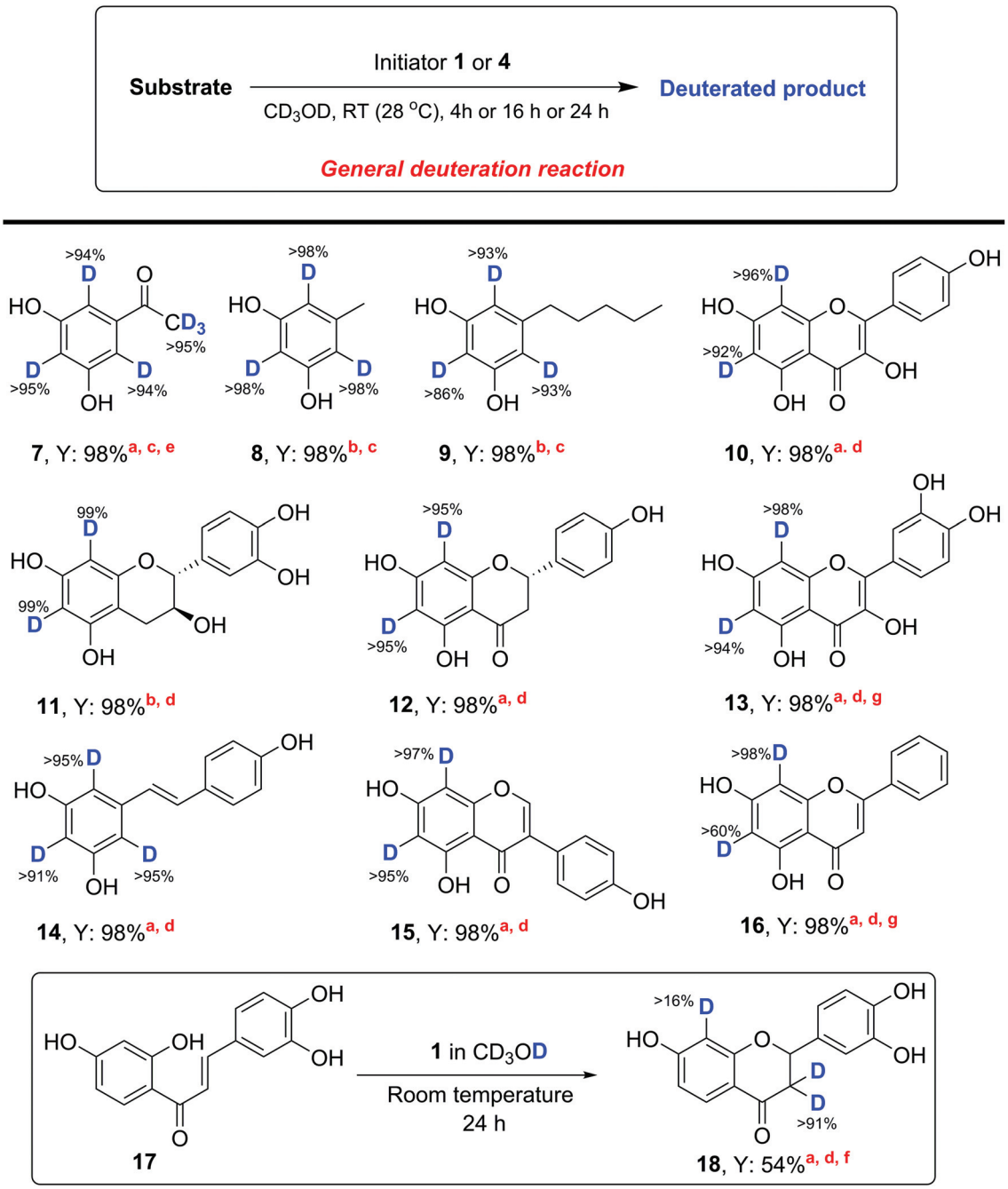



Fig. 2 *In situ* generation of DX from prenyl halides in $CD_3OD$.

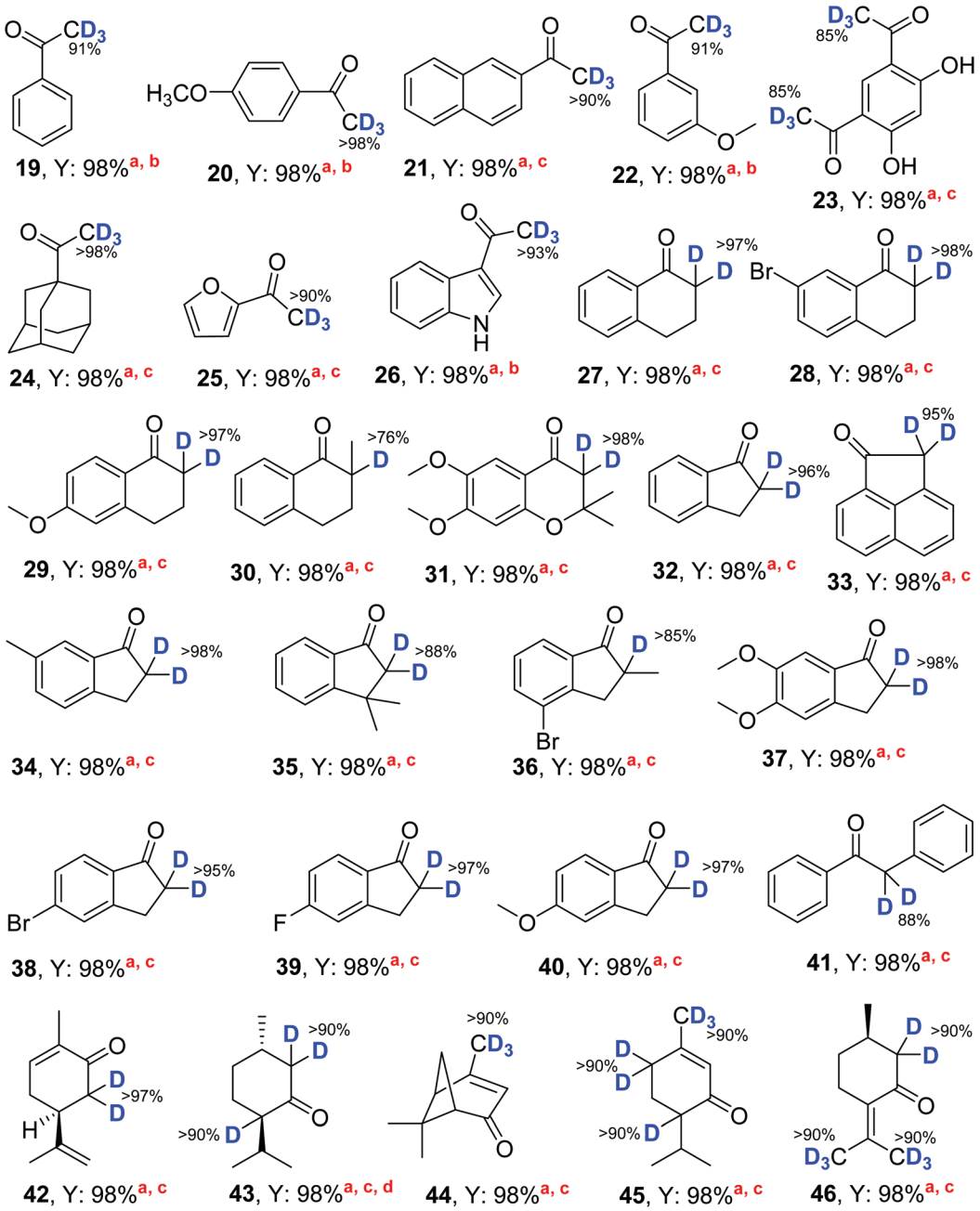
We then performed the deuteration of other phenolic compounds, orcinol (**8**) and olivetol (**9**); at least 86%–98% deuterium incorporation was observed (Scheme 1). The reactions were performed either in an NMR tube or a small flask with 20–40 mg of substrates, and the deuterated products were simply obtained after evaporation without using chromatographic separation. We then explored natural phenolic compounds, flavonoids and stilbenes, which have been widely studied in research because they exhibit various biological activities.[50–52] Deuterated flavonoids and stilbenes, kaempferol (**10**), catechin (**11**), naringenin (**12**), quercetin (**13**), resveratrol (**14**), and genistein (**15**) were obtained with 91%–99% deuterium incorporation at the aromatic protons of ring A, using 3 mol% of prenyl bromide (**1**) or 10 mol% of propargyl bromide (**4**) as initiators (Scheme 1). Note that C-6 of chrysin (**16**) had only 60% deuteration. We found that the deuteration of the flavonoids **8**, **9**, and **11** using initiator **1** gave by-products, and therefore the less reactive initiator **4** was used for deuteration. For a non-polar flavonoid, *i.e.* chrysin (**16**), THF could be used as a co-solvent in order to increase the solubility of the substrate. Interestingly, a stilbene butein (**17**) was cyclized to a natural flavanone, butin (**18**) (54% yield) and >91% deuterium incorporation was observed at the C-3 position of the flavanone and >16% at the C-8 position of an aromatic ring (Scheme 1). This cyclization likely occurred *via* an acid-mediated reaction. Recently, a mild method for the deuteration of aromatic compounds assisted by a keto-enamine tautomeric intermediate was reported.[40] The present method gives similar deuteration positions of phenolic compounds and the deuterated products are obtained without chromatographic separation. Since clinical trials of flavonoids and stilbenes are widely studied because of their potential applications in many aspects,[53,54] there were pharmacokinetics studies of these compounds using LC/MS analysis.[53,55,56] Deuterium-labelled flavonoids and stilbenes prepared from this simple method can be used as internal standards in LC/MS analysis.

Deuteration at the position next to the carbonyl of the flavanone, butin (**18**), as well as at the methyl group of **7** (Scheme 1), suggested that our method may be applicable for carbonyl compounds. Indeed, a methyl group next to a carbonyl group of compounds **19–26** was deuterated with 85%–98% deuterium incorporation (Scheme 2). The methyl ketone of substrates with adamantane, furan, and indole functional




**Scheme 1** General deuteration reaction and structures of initiators **1–4** and the deuteration of phenolic compounds. The reaction was performed at room temperature (28 °C) with 20–40 mg (0.1–0.3 mmol) of each substrate. [a] Initiator **1** (3 mol%) in $CD_3OD$; [b] initiator **4** (10 mol%) in $CD_3OD$; [c] 16 h reaction time; [d] 24 h reaction time; [e] mesitylene as an internal standard; [f] purification by $C_{18}$ HPLC; and [g] THF as a co-solvent.

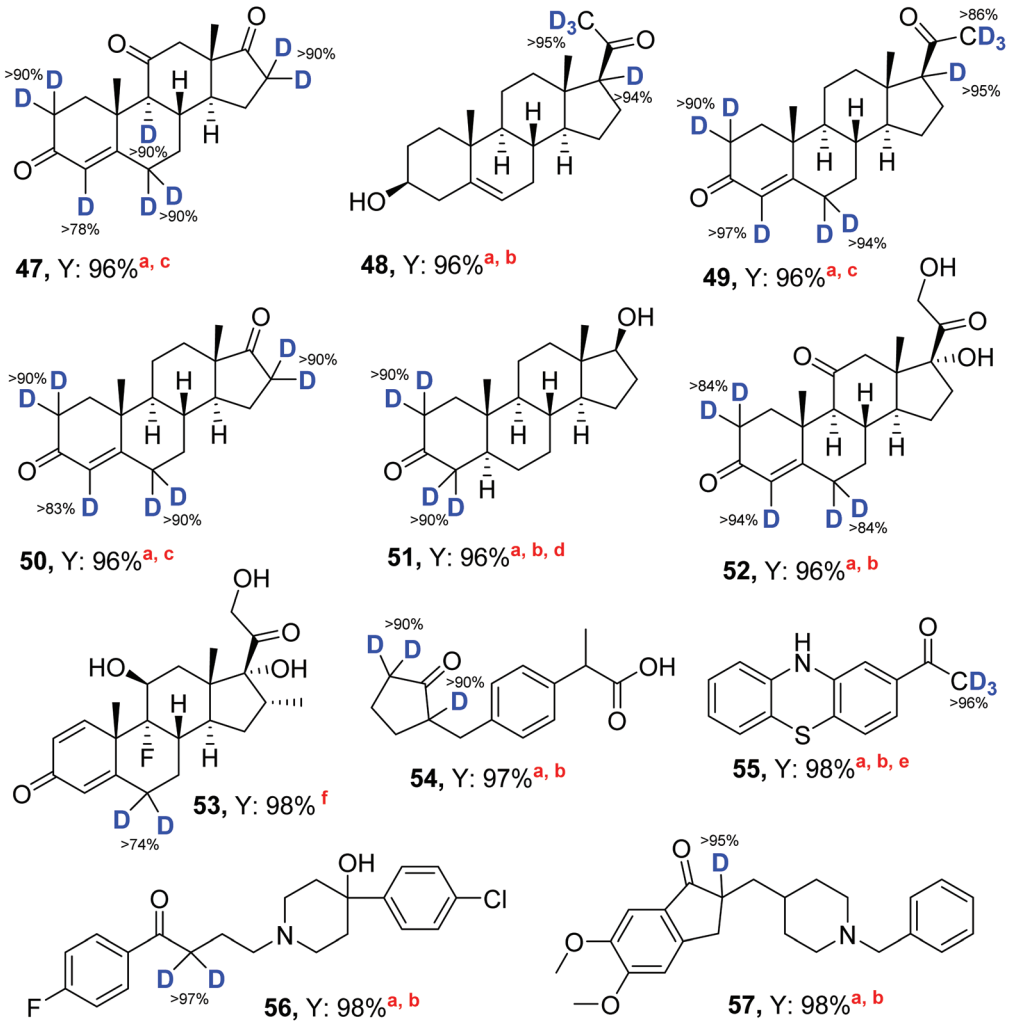
groups, *i.e.* compounds **24–26**, was deuterated with up to 90%–98% deuterium incorporation (Scheme 2). The deuteration of the methylene protons of tetralone derivatives (**27–29**) was observed with >97% deuterium incorporation. However, unlike the methylene protons in **27–29**, a lower rate of H/D exchange (>76%) for a methine proton next to a carbonyl group was observed for a tetralone **30**. The H/D exchange of a methylene group of chroman-4-one (**31**) was >98%, while protons next to a carbonyl in a five-membered ring of **32–40** exhibited 85%–98% deuteration (Scheme 2). It is worth mentioning that the *ortho* deuteration observed in phenols (Scheme 1) is not observed for anisole derivatives (Scheme 2). Methylene protons of 2-phenylacetophenone (**41**) underwent 88% deuteration. Natural monoterpenes, (*S*)-(+)-carvone (**42**), (+)-menthone (**43**), (1*S*)-(−)-verbenone (**44**), (−)-piperitone (**45**), and (+)-pulegone (**46**), were used as substrates for deuteration.




**Scheme 2** Deuteration of carbonyl compounds. Reaction was performed at room temperature (28 °C) with 20–40 mg (0.1–0.3 mmol) of each substrate. [a] Initiator **1** (3 mol%) in $CD_3OD$; [b] 4 h reaction time; [c] 16 h reaction time; and [d] a mixture of two diastereomers.

Methylene protons or methine protons next to a carbonyl group of **42**, **43**, **45**, and **46** were deuterated with >90% deuterium incorporation (Scheme 2). Unexpectedly, the methyl protons of **44–46** and the methylene protons of **45** that were 3 bonds away from a carbonyl group (γ position) were deuterated with >90% deuterium incorporation (Scheme 2). It is worth mentioning that, unlike those in **43** and **45**, the $sp^3$ methine proton next to a carbonyl group of **44** was not deuterated. A single enantiomer (+)-menthone (**43**) was used as a substrate; however, there were two diastereomers obtained after the reaction (Scheme 2), suggesting that deuterium incorporation occurred at both the α- and β-faces of the methine proton next to a carbonyl group. Previously, $d_8$-labeled pulegone (**46**) was prepared using sodium metal (Na) and $CH_3OD/D_2O$, followed by chromatographic separation.[57] The present work provides a simple metal-free preparation of $d_8$-labeled pulegone (**46**).

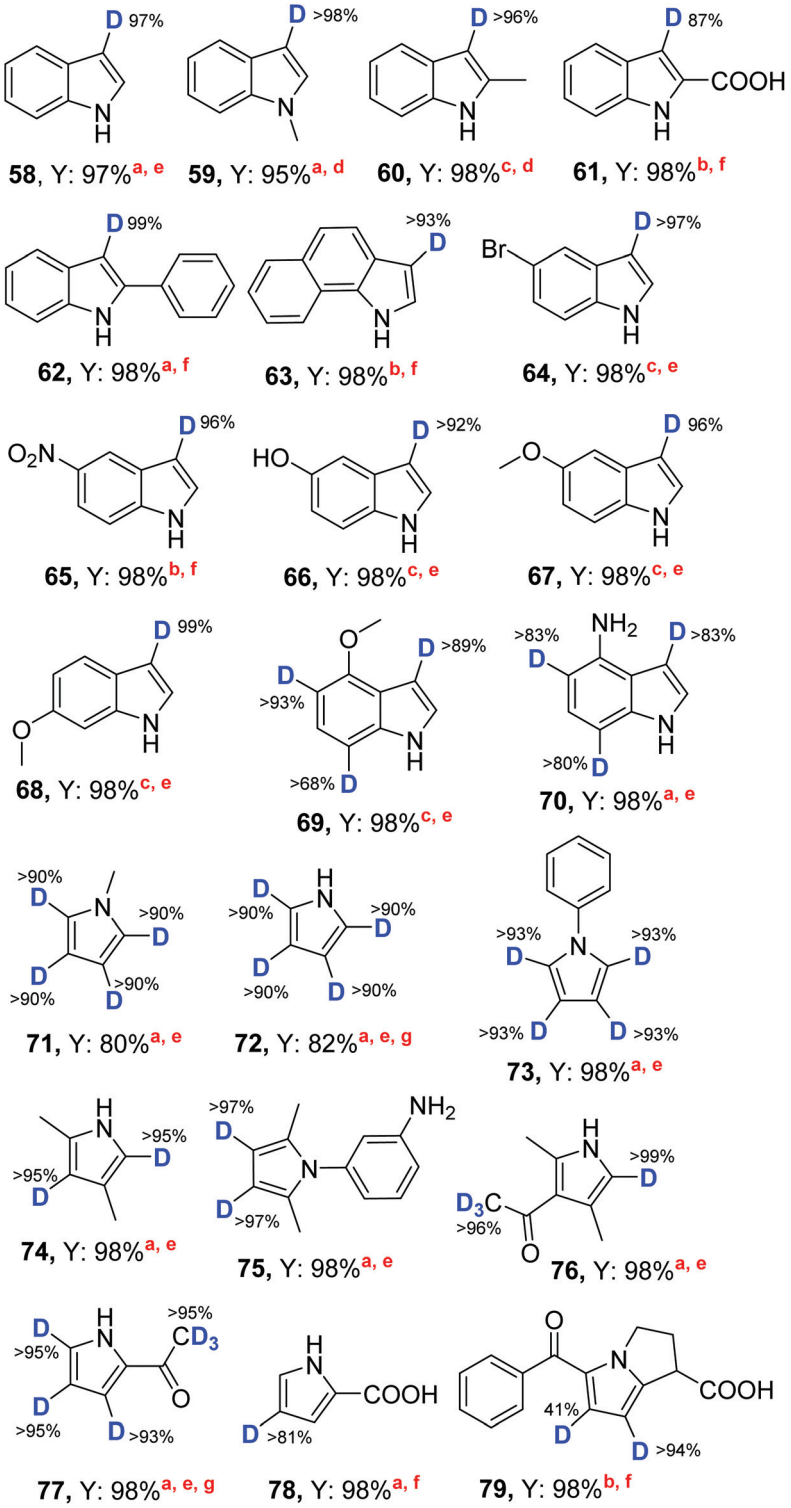
Many FDA-approved drug molecules are carbonyl compounds, and some drugs were selected for the H/D exchange experiment (Scheme 3). Next, we used steroid drugs and drugs with carbonyl groups as substrates. Steroid drugs include adre-




**Scheme 3** Deuteration of steroids and drugs with a carbonyl group. Reaction was performed at room temperature (28 °C) with 20–40 mg (0.1–0.3 mmol) of each substrate. [a] Initiator **1** (3 mol%) in $CD_3OD$; [b] 16 h reaction time; [c] 24 h reaction time; [d] $CHCl_3$ as a co-solvent; [e] THF as a co-solvent; and [f] initiator **2** (3 mol%) in $CD_3OD$ for 48 h.

nosterone (**47**), pregnenolone (**48**), progesterone (**49**), Δ4-androstene-3,17-dione (**50**), stanolone (**51**), cortisone (**52**), and dexamethasone (**53**), while other drugs are loxoprofen (**54**), 2-acetylphenothiazine (**55**), haloperidol (**56**), and donepezil (**57**) (Scheme 3). A metal-free preparation of deuterated drugs resulted in a deuterium incorporation of 78%–97% for steroid drugs **47**–**52**. Dexamethasone (**53**) could not be deuterated by prenyl bromide (**1**); however, deuteration of **53** was achieved by prenyl chloride (**2**), resulting in 74% deuterium incorporation (Scheme 3). It is worth mentioning that dexamethasone (**53**) has been recently found to be useful for the treatment of patients hospitalized with COVID-19.[58] H/D exchanges were observed at the α- and γ-positions next to the carbonyl groups of steroids **47**, **49**, **50**, **52**, and **53** (Scheme 3). Deuteration of other drugs with a carbonyl group (**54**–**57**) was achieved with 90%–97% deuterium incorporation (Scheme 3). Recently, an efficient deuteration at the α-position of carbonyl-based pharmaceutical compounds was reported using a Lewis acid and $D_2O$;[34] however, our method gave a slightly higher % of deuterium incorporation for $d_9$-labeled progesterone (**49**), $d_3$-labeled loxoprofen (**54**), $d_2$-labeled haloperidol (**56**), and $d_1$-labeled donepezil (**57**). Previously, $d_8$-labeled Δ4-androstene-3,17-dione (**50**) was prepared by a two-step method, first with a Rh catalyst under $D_2$ gas, followed by the use of NaOD/$D_2O$ at 65 °C,[59] while $d_3$-labeled pregnenolone (**48**) was synthesized by the following two-step method: first treating with NaOD in $D_2O$ and then with DCl.[60] The present method provides a single step without a purification process for the preparation of **48** and **50**. A number of methods have been reported for the deuteration of carbonyl compounds using metals (*i.e.* Pd, Rh, and Ir),[30–33] organocatalysts,[35–37] microwave-assisted deuteration,[38] and antibody.[39] α-Deuterated carbonyl compounds could also be prepared from enolates using MeLi/$CD_3COOD$.[61] These methods, except that with an antibody as a catalyst, require harsh reaction conditions, and they employ chromatographic separation.

Heteroarenes were the next target group of compounds for a study on substrate scope, and we found that indoles and pyrroles could be deuterated by initiators **1** and **4** (Scheme 4). Position 3 of indoles **58–68** was selectively deuterated with a deuterium incorporation of 87%–99%, and the electron withdrawing or donating group on the aromatic ring of indoles did




**Scheme 4** Deuteration of heteroarenes, indoles and pyrroles. Reaction was performed at room temperature (28 °C) with 20–40 mg (0.1–0.3 mmol) of each substrate. [a] Initiator **1** (1 mol%); [b] initiator **1** (3 mol%); [c] initiator **4** (10 mol%); [d] 15 min reaction time; [e] 16 h reaction time; [f] 24 h reaction time; and [g] mesitylene as the internal standard.

not have much effect on the deuteration (Scheme 4). However, the amount (3 mol%) of the initiator **1** used for the deuteration of indoles with electron withdrawing groups, *i.e.* compounds **61**, **63**, and **65**, was slightly higher than that (1 mol%) used for other indoles (Scheme 4). Moreover, some indoles, *i.e.* compounds **60**, **64**, and **66–69**, were very reactive toward the initiator **1**, giving by-products; therefore, the less reactive initiator, propargyl bromide (**4**), was used for the deuteration of these indoles (Scheme 4). Interestingly, the deuteration of 4-substituted indole derivatives gave $d_3$-labeled indole derivatives **69** and **70**, whereby two additional aromatic protons were deuterated with a deuterium incorporation of 68%–93% (Scheme 4). Deuteration of pyrroles was easily achieved by the initiator **1**, giving $d_4$-labeled pyrrole derivatives **71–73** with a deuterium incorporation of 90%–93%, as well as $d_2$-labeled pyrroles **74** and **75** with a deuterium incorporation of 95%–97% (Scheme 4). Note that the yields of **71** (b.p. 112–113 °C) and **72** (b.p. 129 °C) were 80% and 82%, respectively; this is because both compounds have low boiling points, and evaporation under vacuum led to loss of compound yields. As expected, the methyl groups of pyrroles with a ketone carbonyl functional group were deuterated giving $d_4$- and $d_6$-labeled pyrroles **76** and **77**, respectively, with a deuterium incorporation of 93%–99%. However, unlike other pyrroles, compound **78** gave a $d_1$-labeled derivative; only position 4 of **78** was deuterated with 81% deuteration (Scheme 4). We then applied our method to the deuteration of ketorolac (**79**), a nonsteroidal anti-inflammatory drug (NSAID). Two positions on a pyrrole ring of drug **79** were deuterated with a deuterium incorporation of 41% and 94% (Scheme 4).

Next, we performed a gram-scale chromatography-free synthesis of deuterated compounds using 1 mol% of the initiator **1**. Deuteration of 1 gram of naringenin (**12**) (dissolved in 8 mL of $CD_3OD$) was achieved with 95% deuterium incorporation. For deuteration of 2.7 grams of naringenin (**12**), THF was used as a co-solvent (5 mL of $CD_3OD$ and 3mL of THF), giving the deuterated product **12** with 80% deuterium incorporation. Deuteration of 1 gram of progesterone (**49**) was performed in 10 mL of $CD_3OD$, giving the deuterated product **49** with 86%–97% deuterium incorporation, while deuteration of 1 gram of a pyrrole **73** was performed in 6 mL of $CD_3OD$, giving a deuterated product **73** with 94% deuterium incorporation. Next, we preliminarily investigated the minimum amount of the initiator required for deuteration. A carbonyl compound **20** required at least 0.5 mol% of the initiator **1** for deuteration with 82% deuterium incorporation, while the indole **60** and pyrrole **71** required only 0.1 mol% of the initiator **1**, giving $d_1$-labeled indole **60** with 97% deuterium incorporation and $d_4$-labeled pyrrole **71** with 81%–87% deuterium incorporation. Therefore, low catalyst loading of initiator **1** is required for deuteration.

Since $CH_3OD$ is relatively inexpensive than $CD_3OD$, we attempted to perform deuteration using $CH_3OD$ as the D source with 3 mol% of initiator **1**. Experiments were performed with two model compounds, 4′-methoxyacetophenone (**20**) and 5-nitroindole (**65**). When using $CH_3OD$ as the D source, the methyl protons next to the carbonyl position of compound **20** were deuterated at >95%, which is similar to that (>96%) using $CD_3OD$. However, deuteration of compound **65** using $CH_3OD$ exhibited a slightly lower percentage of deuteration (>86%) than that (>96%) using $CD_3OD$. Therefore, $CD_3OD$ may enable slightly better H/D exchange than $CH_3OD$ for particular substrate types. However, $CH_3OD$ is much less expensive than $CD_3OD$.

The proposed mechanism for the deuteration of phenolic compounds, carbonyl compounds and steroids, and indoles is depicted in Fig. 3. Deuteration is catalyzed by deuterium halide (DX), which is *in situ* generated from prenyl halides in $CD_3OD$ (Fig. 3A). For phenolic compounds, DX catalyzes the formation of the intermediate PI, which in turn undergoes proton (H) abstraction by the X ion to give a deuterated product (Fig. 3B). Due to the kinetic isotope effect, the C–D bond is more stable than the C–H bond; therefore, H abstraction by X ions from intermediate PI occurs, giving a deuterated product (Fig. 3B). In the case of carbonyl compounds or steroids (Fig. 3C), DX attacks a carbonyl to form an intermediate S1, which in turn, undergoes H abstraction by X ions, giving its enol form S2. Then, DX catalyzes the insertion of a D atom into S2 to give the intermediate S3, which in turn converts into a deuterated product by D abstraction by X ions (Fig. 3C). For indoles, DX catalyzes the insertion of a D atom into an indole molecule to form an intermediate DI, and a proton from DI is abstracted by the X ion due to the kinetic isotope effect mentioned earlier, giving a deuterated product (Fig. 3D). As shown in the deuteration mechanisms of these compounds, HX is generated due to the H/D exchange between DX and individual substrates. It is interesting to mention that DX is regenerated from HX in the presence of an excess amount of $CD_3OD$, as depicted in Fig. 3E. To clearly explain how catalytic amounts of initiators could efficiently catalyze deuteration, DBr obtained by *in situ* generation from prenyl bromide (**1**) is used as a model initiator (Fig. 3F). First, *in situ* generation of DBr along with compounds **5** and **6** occurs in $CD_3OD$. During the deuteration reaction, H/D exchange between the DX and individual substrate leads to the generation of HBr, which in turn undergoes H/D exchange with excess $CD_3OD$ to give DBr that is readily utilized for further deuteration (Fig. 3F). So far, *in situ* generation of DX from organic compounds has never been reported, and the spontaneous transformation of prenyl halides to DX presented in this work could be useful for organic chemistry. Although *in situ* generation of hydrogen iodide (HI) was previously reported for the preparation of α-glycosyl iodides and vicinal iodohydrins, HI was generated from molecular iodine ($I_2$).[62]

Generation of DX from initiators **1–4** has never been reported so far. It is known that *in situ* generation of HCl from acetyl chloride in $CH_3OH$ occurs through a nucleophilic attack on a carbonyl carbon of acetyl chloride by $CH_3OH$, giving HCl and methyl acetate ester.[63] We performed deuteration using acetyl chloride in $CD_3OD$ with 4′-methoxyacetophenone (**20**) as a model substrate (ESI†). It was found that acetyl chloride could promote the deuteration of **20** with >95% incorporation

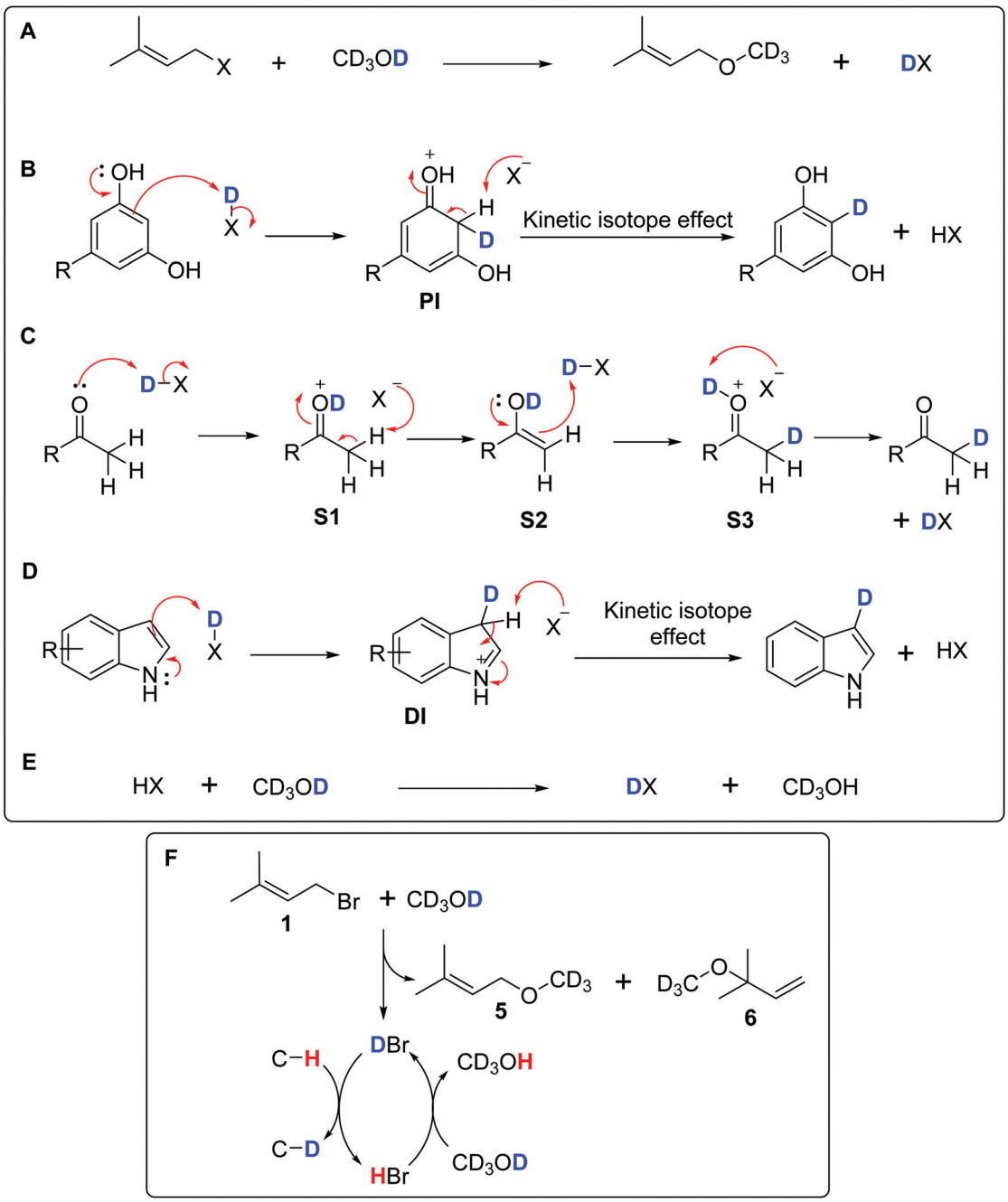



**Fig. 3** *In situ* generation of DX from prenyl halides in $CD_3OD$ (A); the proposed deuteration mechanism of phenolic compounds (B), carbonyl compounds and steroids (C), and indoles (D); regeneration of DBr from HBr during deuteration in the presence of excess $CD_3OD$ (E); and *in situ* generation of DBr from prenyl bromide (**1**) and H/D exchange of substrates and excess $CD_3OD$ (F).

of deuterium, indicating that DCl was generated in this system. DCl is commercially available (20% solution in $D_2O$), and indeed, we found that compound **20** was deuterated by DCl with >95% incorporation of deuterium. Although deuteration by acetyl chloride or commercial DCl is anticipated, a simple generation of deuterium (hydrogen) halide from initiators **1–4** is unprecedented. Although DCl is commercially available, it is much more expensive than the initiators used in this work. Moreover, commercial DCl is available in 20% solution in $D_2O$, which may cause problems for the reaction that is sensitive to water.

Commercial reagent **1** contains silver wool as a stabilizer, while **2** does not have any stabilizer. In order to exclude the involvement of metal traces in the generation of DX from prenyl halides, initiator **1** that contains silver wool as the stabilizer was distilled under vacuum using Kohguller apparatus prior to use in deuteration. TMS-free $CD_3OD$ with purity >99.5%, which does not contain any stabilizer, was used in

deuteration. Distilled initiator **1** provided the same deuteration percentages as non-distilled initiator **1** for model compounds, 4′-methoxyacetophenone (**20**) and 5-nitroindole (**65**), indicating that traces of the metal were not involved in the deuteration or generation of acid. Next, we preliminarily explored the effects of light and temperature on deuteration using initiator **1** or acetyl chloride with **20** and **65** as model substrates (ESI†). Deuteration with initiator **1** or acetyl chloride led to >95% or >97% deuteration of **20** or **65** under dark conditions, normal day light, and tungsten light, indicating that deuteration or generation of acid by **1** or acetyl chloride is independent of light. However, when using initiator **1** for deuteration, less than 8% or 2% deuteration of **20** or **65** was observed at −10 °C, while >95% or >97% deuteration for **20** or **65** was observed at room temperature (28 °C) (ESI†), suggesting that the generation of DBr from **1** depends on temperature. When using acetyl chloride for deuteration, >95% or >97% deuteration of **20** or **65** was achieved at both −10 °C and room temperature; this indicates that deuteration by acetyl chloride did not depend on temperature. In conclusion, the spontaneous conversion of prenyl halides to acids is temperature dependent, but independent of light, while the nucleophilic substitution mechanism for the generation of DCl of acetyl chloride is independent of both light and temperature.

The spontaneous conversion of prenyl halides to acids at room temperature (28 °C) is unprecedented. Next, we explored the ability of cinnamyl bromide (**80**), an aromatic substituted allylic halide, to generate DBr. It was found that cinnamyl bromide (**80**) could be used for deuteration (ESI†). It is proposed that the generation of acid from cinnamyl bromide (**80**) in $CD_3OD$ should be analogous to that of prenyl halides as shown in Fig. 2, from which compounds **5** and **6** are formed; therefore, the products **81** and **82** (Fig. 4) should be produced from the spontaneous conversion of cinnamyl bromide (**80**) to acid. Indeed, the $^1$H NMR spectra of cinnamyl bromide (**80**) in $CD_3OD$ at different time intervals of 0 h, 0.5 h, 1 h, 3 h, 6 h and 24 h (Fig. 5) revealed that derivatives **81** and **82** are formed. The product **81** was the major compound, while **82** was the minor product (Fig. 5). The $^1$H and $^{13}$C NMR resonances of a methylene group of cinnamyl bromide (**80**) were at $\delta_H$ 4.16 and $\delta_C$ 34.01, while those of the product **81** were at $\delta_H$ 4.07 and $\delta_C$ 73.97 (ESI†). The $^{13}$C NMR resonance of a carbon of the $-OCD_3$ moiety in **81** was at $\delta_C$ 57.0 with characteristics of a carbon bearing D atom, and the HMBC spectrum showed the correlation from methylene protons ($-CH_2$-O) to this carbon (ESI†). The exo-methylene protons of the product **82** resonated at $\delta_H$ 5.20 (Fig. 5). We evaporated $CD_3OD$ from a sample of **81** and changed the NMR solvent from $CD_3OD$ to $CDCl_3$; we observed the presence of cinnamyl bromide (**80**) in a sample of **81** (ESI†), indicating that a portion of **81** was converted back to **80** possibly during the evaporation of $CD_3OD$. The proposed mechanism for the spontaneous conversion of

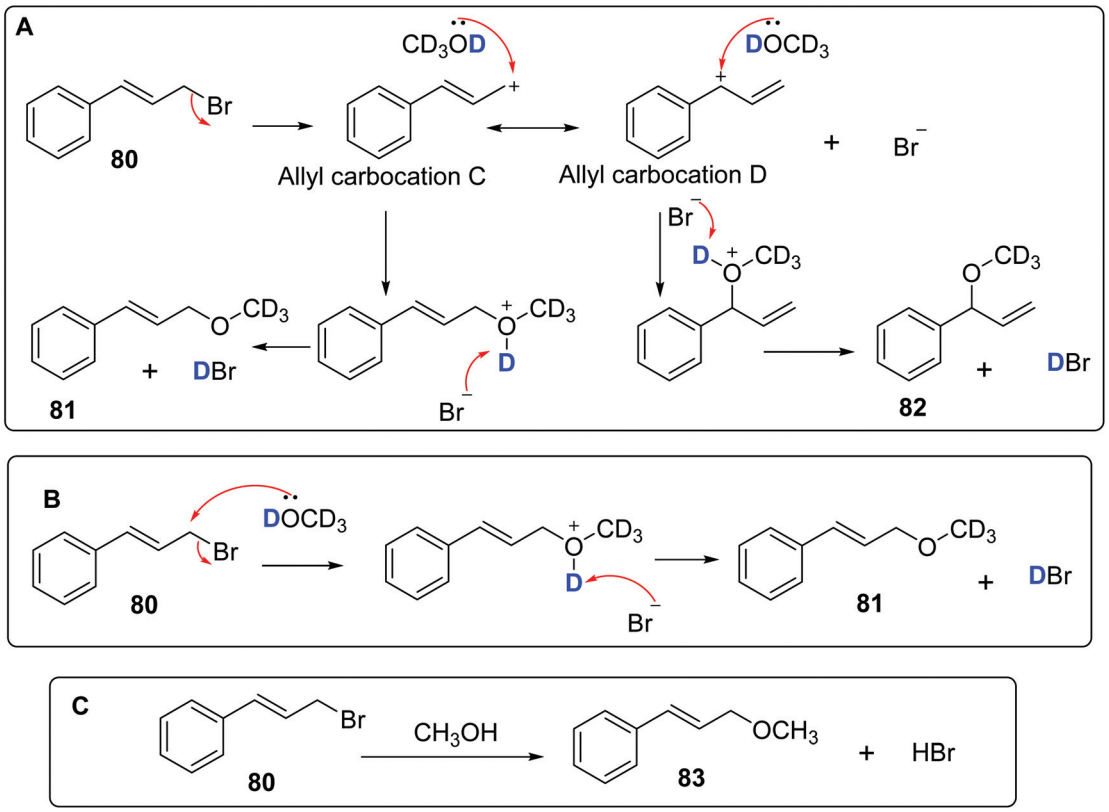



**Fig. 4** Proposed mechanism for the spontaneous conversion of cinnamyl bromide (**80**) to DBr and compounds **81** and **82** in $CD_3OD$. (A) $S_N1$ reaction mechanism, (B) $S_N2$ reaction mechanism, and (C) conversion of cinnamyl bromide (**80**) to ether **83** in $CH_3OH$ (C).

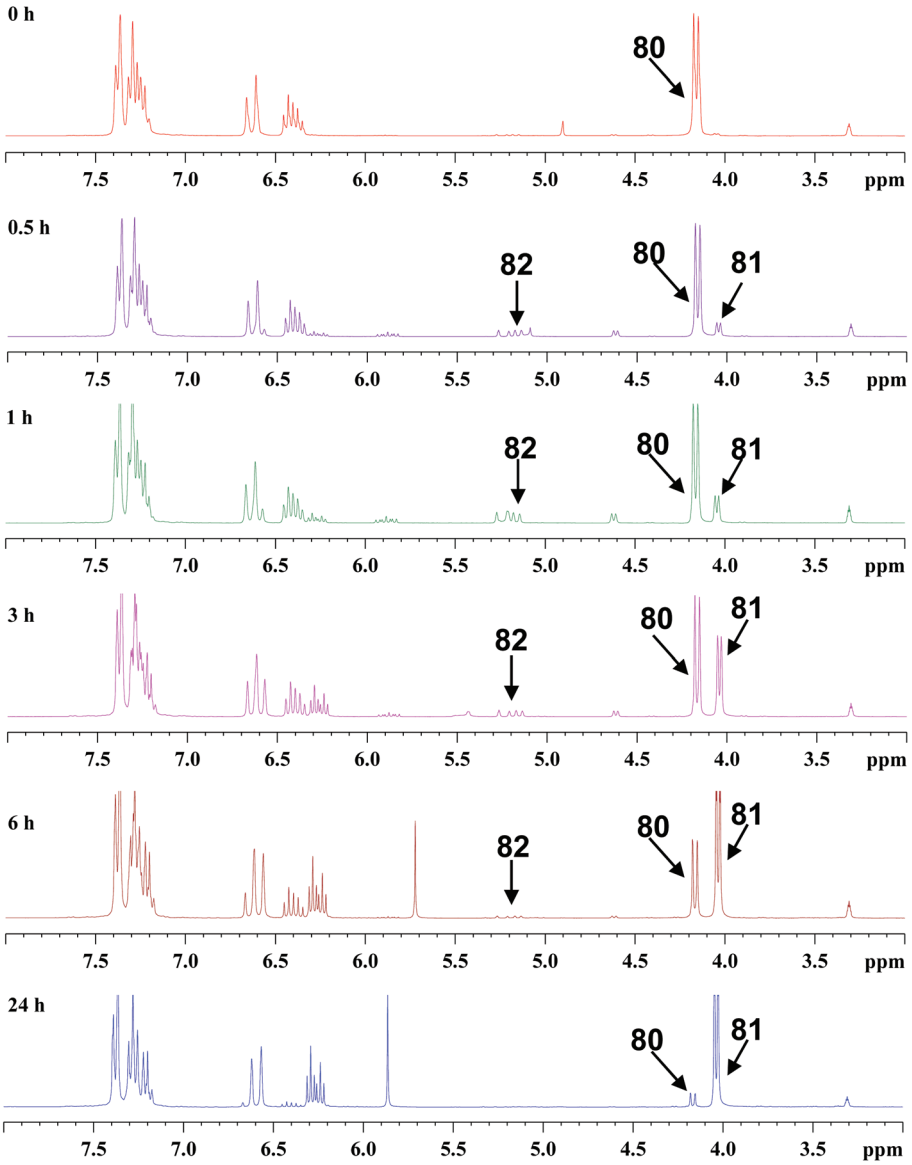



**Fig. 5** $^{1}$H NMR spectral overlay of cinnamyl bromide (**80**) (50 mg) in $CD_3OD$ (0.6 mL) at different time intervals of 0 h, 0.5 h, 1 h, 3 h, 6 h and 24 h, indicating the spontaneous conversion of **80** to compounds **81** and **82** at room temperature.

cinnamyl bromide (**80**) to the products **81** and **82** could be through the $S_N1$ reaction mechanism (Fig. 4A) or the $S_N2$ reaction mechanism (Fig. 4B). For the $S_N1$ type reaction mechanism, the allyl carbocation C is first generated from cinnamyl bromide (**80**) after the departure of a Br ion as a leaving group, and the allyl carbocation C undergoes delocalization of π-electrons to give the allyl carbocation D (Fig. 4A). Both allyl carbocations C and D react with $CD_3OD$ to give oxonium ions, which in turn react with Br ions to give DBr and compounds **81** and **82** (Fig. 4A). Since the allyl carbocation D (tertiary carbocation) is more stable than the allyl carbocation C (primary carbocation), compound **82**, which is generated through the allyl carbocation D, is anticipated to be produced in a higher ratio than compound **81** that is generated from the less stable allyl carbocation C (Fig. 4A). However, compound **81**, which is generated *via* the carbocation C, was observed in a higher ratio than compound **82** that is generated *via* the carbocation D; this suggests that the mechanism favors the $S_N2$ type of reaction rather than $S_N1$ (Fig. 4B). For the $S_N2$ mechanism, the departure of the leaving group Br and attack by $CD_3OD$ simultaneously occur to give oxonium ions, which in turn react with Br ions to give DBr and compound **80** (Fig. 4B). Although the reaction mechanism *via* the $S_N2$ type of reaction was favorable over that through the $S_N1$ mechanism, a small amount of compound **82** was also observed in the $^{1}$H NMR spectrum, suggesting that the $S_N1$ type reaction mechanism may also occur to some extent. Previously, similar allyl cation intermediates for indole alkylation were generated from dimethylallyl diphosphate using a strong acid, $H_2SO_4$,[64] whose proposed mechanism is similar to the $S_N1$ mechanism shown in Fig. 4A. When cinnamyl bromide

(**80**) is dissolved in $CH_3OH$ and left stirring at room temperature for 24 h, it was found that a portion of **80** spontaneously transformed to ether **83** (Fig. 4C) (ESI†).

The mechanism for the spontaneous transformation of prenyl halides and cinnamyl bromide (**80**) to acid is not conclusively established in this work. This unnoticed chemistry discovered in this work needs further studies on the detailed mechanism, both on theoretical and experimental aspects. Moreover, there is room for research to explore this chemistry for other applications, not only for deuteration presented in this work. However, safety precautions on acid DX or HX generated from the reaction should be considered when applying this method for research or industry. We would like to coin the name "Anichcha reaction" for the spontaneous reaction of prenyl halides to acid, in order to describe the impermanent nature of compounds **1–4** and cinnamyl bromide (**80**). The word "Anichcha" is derived from Buddhist philosophy, which describes impermanence or instability or change and uncertainty of everything.

## Conclusions

In summary, we found a new method for *in situ* generation of acid DX or HX under mild conditions using inexpensive reagents in a laboratory, prenyl halides (**1** and **2**), allyl bromide (**3**) and propargyl bromide (**4**). Deuterium halides were generated in $CD_3OD$, and the present work demonstrated the use of deuterium halides for acid-catalyzed deuteration. This work provides a simple metal-free preparation of deuterated compounds with a broad substrate scope. The generation of the acids (DBr or DCl) presented here may be applied for other reactions, *i.e*. acid-catalyzed reactions. It is known that deuterium isotope effects have influence on organic reactions; therefore, deuterium halides generated from initiators **1–4** may yield products which are different from other acid-catalyzed reactions using common acids. This overlooked chemistry may be useful for future research in organic chemistry.

## Author contributions

D.D.: investigation, formal analysis, and writing – original draft; S.S.: investigation; C.M.: supervision; S.R.: supervision and funding acquisition; P.K.: conceptualization, writing – original draft, writing – review and editing.

## Conflicts of interest

The authors declare no competing interests.

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