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Selective oxidation of alcohol-d_1 to aldehyde-d_1 using MnO_2†

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The selective oxidation of alcohol-d_1 to prepare aldehyde-d_1 was newly developed by means of $NaBD_4$ reduction/activated MnO_2 oxidation. Various aldehyde-d_1 derivatives including aromatic and unsaturated aldehyde-d_1 can be prepared with a high deuterium incorporation ratio (up to 98% D). Halogens (chloride, bromide, and iodide), alkene, alkyne, ester, nitro, and cyano groups in the substrates are tolerated under the mild conditions.

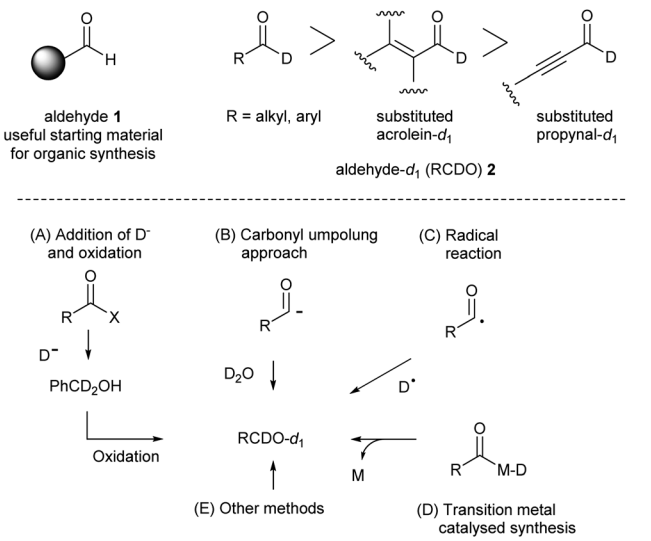
1. Introduction

Deuterium (^{2}H, d) is a stable, non-radioactive, and safe isotope of hydrogen (^{1}H). Since its discovery,[1] d has been widely utilized in organic chemistry, biochemistry, analytical chemistry, pharmaceutical science, and drug discovery.[2,3] Because of the high demand for d-labelled molecules in the scientific research fields, many efforts have been devoted to developing a new method for the synthesis of d-labelled molecules.

Aldehyde-d_1 **2** has received significant attention as a synthetic target due to the facts that aldehyde **1** is a useful feedstock in organic synthesis. Various methods have been performed in the synthesis of alkyl and aryl aldehyde-d_1. For example, more than 40 syntheses (25 different reaction conditions) of benzaldehyde-d_1 (PhCDO) were conducted even since 2018 in the studies to develop new d-incorporation method or reaction mechanism using PhCDO.[4–8]

The previous synthetic approaches to access d-labelled molecules are classified into 5 types; (A) addition of D^- followed by oxidation, (B) carbonyl Umpolung approach, (C) radical reaction, (D) transition metal-catalysed reaction, and (E) others. Recently, mild, one-step, and catalytic syntheses of aldehyde-d_1 **2** have been achieved by deuteration of the Breslow intermediates,[9] deuteration of acyl radicals,[6,10] and transition metal-catalysed deuterium incorporation.[11] However, the previous synthetic methods including the modern direct syntheses often suffered from drawbacks such as over-deuteration, requirements of harsh conditions (high and low temperature, and strong base and acids), and the use of expensive catalysts. Moreover, the synthetic examples of substituted acrolein and propynal-d_1 are much less than those of alkyl and aryl aldehyde-d_1,[12,13] though recently developed NHC-catalysed H–D exchange reactions allowed access to various substituted acrolein-d_1 derivatives.[9] In this context, development of a new d-incorporation method which allows flexible synthesis of aromatic and unsaturated aldehyde-d_1 **2** remains to be a challenging synthetic task (Scheme 1).

Method A using D^- as a deuterium source has been recognized as a robust and conventional synthetic method to prepare aldehyde-d_1 **2** (Scheme 2). The synthesis is typically performed



Scheme 1 Synthesis of aldehyde-d_1 derivatives. (A) reduction of the formyl with D^- and oxidation, (B) carbonyl Umpolung approach, (C) radical H–D exchange, (D) transition metal-catalysed H–D exchange, and (E) others.

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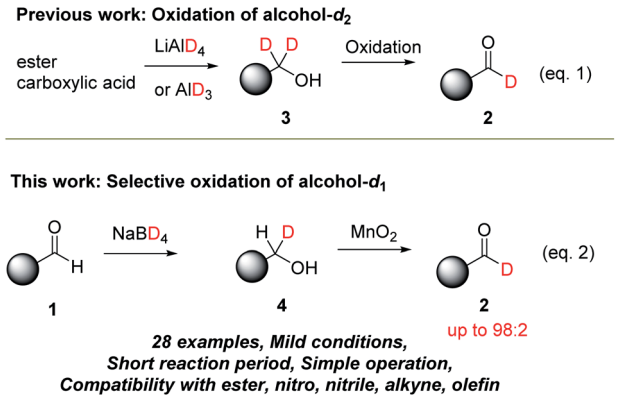


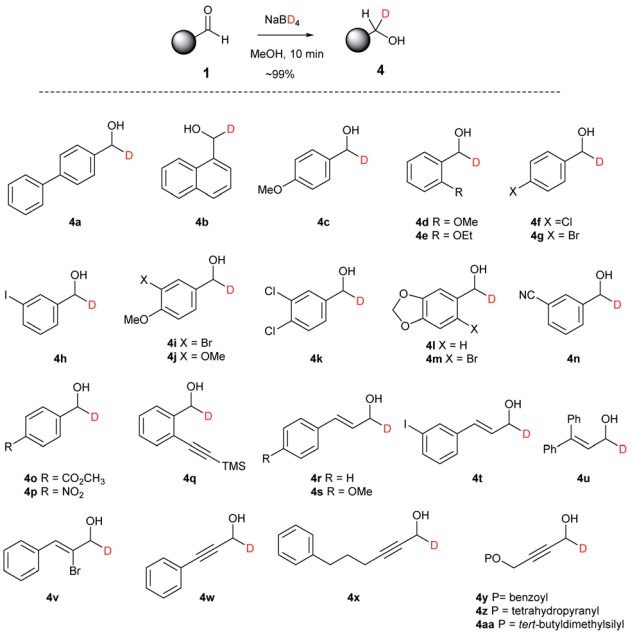
Scheme 2 Oxidation of deuterated alcohols. Eqn (1): oxidation of alcohol-d_2, eqn (2): selective oxidation of alcohol-d_1.

in two steps; (i) reduction of carboxylic acid derivatives using $LiAlD_4$ to provide alcohol-d_2 **3** and (ii) oxidation to aldehyde-d_1 **2** (eqn (1)).[14] In this approach, the deuterium incorporation ratio (%D) of the commercially available D^- sources such as $LiAlD_4$ (>98 atom) is reliably transferred into the product. On the other hand, the use of highly reactive $LiAlD_4$ often limits the synthetic scope. Under the conditions, various functional groups such as nitro, nitrile, ester, and acid moieties, and alkene and alkyne with electron-withdrawing group(s) are not tolerated. To overcome the limitation, we emerged selective oxidation of alcohol-d_1 derivatives **4** (Scheme 2(eqn (2))). It is expected that various alcohol-d_1 **4** can be prepared by the mild $NaBD_4$ reduction. The next selective oxidation of D (H/D selectivity) is the key to this approach. Recently, oxidation of benzyl alcohol-d_1 (PhCDHOH) with PCC or PDC was conducted to prepare PhCDO with ~85% D.[4a,4e,4q] On the other hand, further efforts to improve the selectivity (%D) in the selective oxidation have not been well-examined. Herein, we would like to report that $NaBD_4$ reduction followed by activated MnO_2 oxidation ($NaBD_4$/MnO_2 system). The simple and mild protocol allows expansion of the synthetic range of aldehyde-d_1 **2** including not only aromatic aldehyde-d_1 derivatives but also substituted acrolein-d_1 and propynal-d_1 derivatives with high %D (up to 98%).

2. Results and discussion

In a similar manner to the previous synthetic examples of $NaBH_4$ reduction of aldehyde **1**, the reduction with $NaBD_4$ gave the corresponding alcohol-d_1 derivatives **4** with excellent functional group compatibility and yields (Scheme 3). Chloride, bromide, iodide, methoxy, ethoxy, or methylene acetal, nitrile, ester, nitro, and alkyne groups on the aromatic ring of **4c–4q** were tolerated under the conditions. Substituted acrolein and propynal **1r–1aa** also underwent smooth $NaBD_4$ reduction to provide **4r–4aa** without loss of the alkyne and alkene moieties, and tetrahydropyanyl (THP), benzoyl (Bz), and *tert*-butyldimethylsilyl (TBS) protecting groups.

We next examined the key oxidation of alcohol-d_1 **4** using 4-phenylbenzyl alcohol-d_1 (**4a**) (Table 1). As a result, activated MnO_2 was found to be superior to other general oxidation



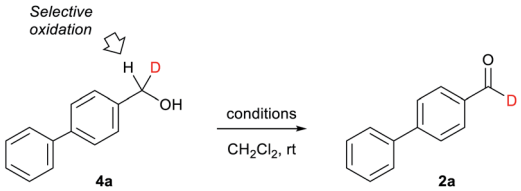
Scheme 3 Reduction of aldehyde **1** with $NaBD_4$.

reagents (entry 1, Table 1). Treatment of **4a** with 23 eq. of MnO_2 in CH_2Cl_2 gave aldehyde-d_1 **2a** with 92% D in 2 h. The use of pyridinium dichlorochromate (PDC) gave **2a** in good selectivity (88% D).[4e] However, the isolate yield was moderate (entry 2). Dess–Martin periodinane oxidation, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) oxidation in the presence of $PhI(OAc)_2$, and Parikh–Doering oxidation (sulfur trioxide–pyridine complex in dimethyl sulfoxide (DMSO)) resulted in lower selectivities (74, 76 and 66%D, entries 3–5).

Activated MnO_2 oxidation was successfully expanded to the synthesis of various aldehyde-d_1 **2a–2aa** with high %D (85–96% D) (Scheme 4A–C). Chloride, bromide, iodide, methoxy, ethoxy, or methylene acetal, nitrile, ester, nitro, and alkyne groups on the aromatic ring of **4c–4q** are preserved under the mild oxidation conditions (Scheme 4A). Substituted acrolein **4r–4v** and propynal **4w–4aa** smoothly underwent MnO_2 oxidation to provide **2r–2aa** without loss of the alkene and alkyne moieties (Scheme 4B and C). The synthetic utility was further demonstrated by the synthesis of **2v** with a bromo group at the α-position of cinnamaldehyde. In addition, Bz, THP, and TBS protecting groups of **4y**, **4z**, and **4aa** were also maintained under the conditions. These propargyl alcohols **4y**, **4z**, and **4aa** were smoothly converted to the corresponding propynal derivatives **2y**, **2z**, and **2aa** with high %D, respectively.

In conjunction with our recent efforts toward elucidation of biosynthetic reaction mechanisms of terpene synthases using d-labelled prenols,[15,16] we needed geranylgeraniol-d_2 (**6**) as an enzyme substrate. Previously, the synthesis of **6** (ref. 17) and other acyclic prenol-d_2 derivatives[18] was performed in four steps from **5** *via* reduction of ester **7** with $LiAlD_4$. However, commercially available $LiAlD_4$ is almost out of stock in recently years. In addition, low temperature conditions (−20 °C) is required for the $LiAlD_4$ reduction to avoid the undesired 1,4-reduction. We

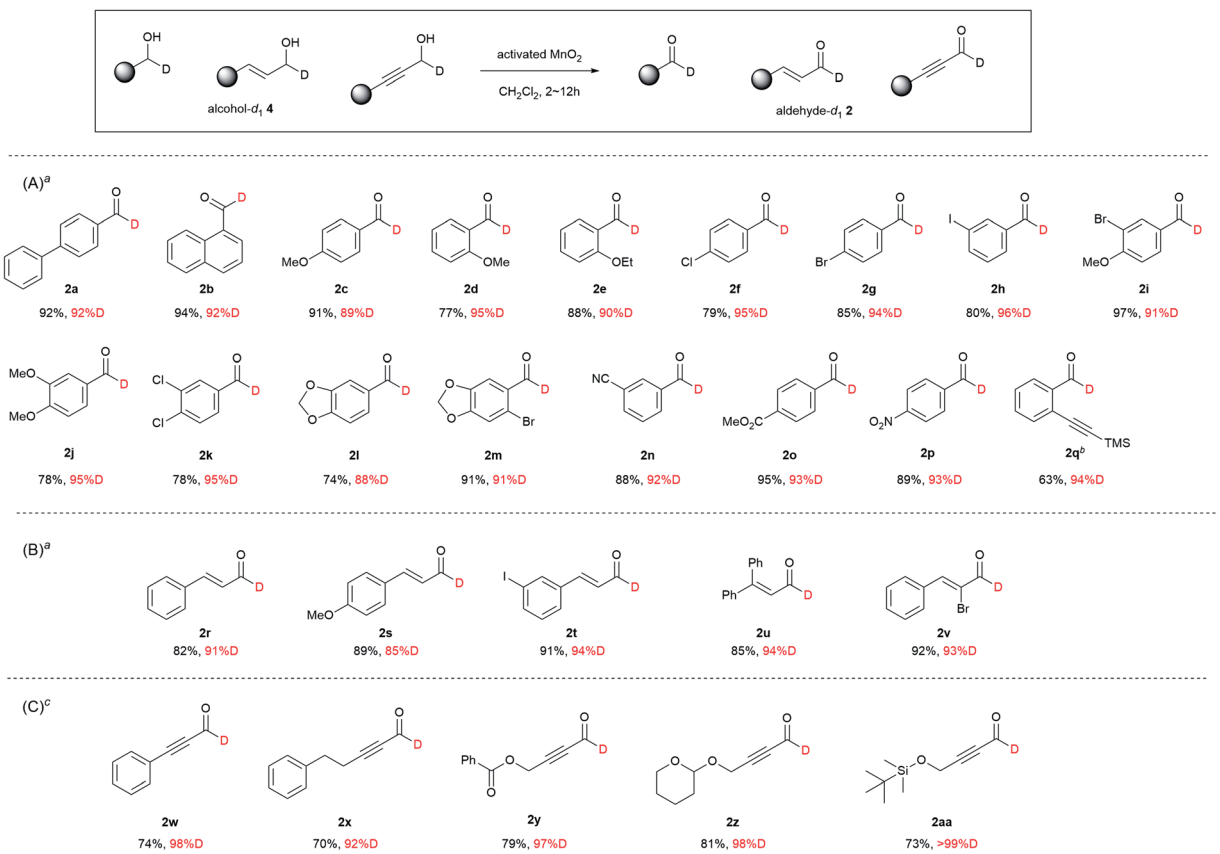
Table 1 Oxidation of alcohol-d_1 **4a**[a]



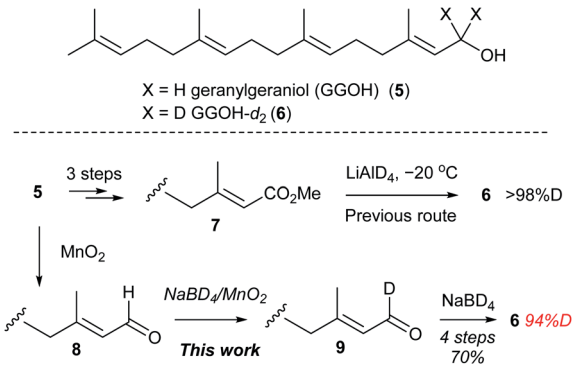
Entry	Conditions	Yield[b] (%)	%D[c]
1	MnO_2 (23 eq.), 1 h	92	92
2	PDC (1.2 eq.), MS4A, 2 h	51	88
3	Dess–Martin periodinane (1.5 eq.), 5 min	84	74
4	TEMPO (0.01 eq.), Bu_4NHSO_4 (0.05 eq.), NaOCl (1.2 eq.), 1 h	96	76
5	DMSO (10 eq.), SO_3–pyridine (4 eq.), iPr$_2$NEt (5 eq.), 1.5 h	75	66

[a] 0.5 mmol scale. [b] Isolated yield. [c] %D for **2a** is calculated based on the integration ratios of aldehyde and aromatic proton. MnO_2 = activated manganese dioxide, PDC = pyridinium dichlorochromate, MS4A = molecular sieves 4A, TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl, DMSO = dimethyl sulfoxide.

expected that $NaBD_4/MnO_2$ system would be an alternative to the $LiAlD_4$ procedure to prepare **6**, conveniently. According to the literature,[19] geranylgeraniol (**5**) was converted to aldehyde **8** by MnO_2 oxidation (Scheme 5). Aldehyde **8** was subjected to $NaBD_4/MnO_2$ to deliver d-enriched aldehyde **9** which was subsequently reduced by $NaBD_4$ to provide geranylgeraniol-d_2 (**6**) in 70% yield over four steps with satisfactory deuterium incorporation ratio (94% D). Under the conditions, the undesired 1,4-addition reaction was not observed. Thus, an



Scheme 4 MnO_2 oxidation of alcohol-d_1 **4**. (A) synthetic examples of aromatic aldehyde-d_1 **2**, (B) synthetic examples of substituted acrolein-d_1 **2**, and (C) synthetic examples of substituted propynal-d_1 **2**. [a]2 h, [b]6 h, [c]12 h.



Scheme 5 Synthesis of geranylgeraniol-d_2 (6) from geranylgeraniol (5).

operationally simple and mild deuteration of prenols-d_2 was achieved by application of $NaBD_4/MnO_2$ system.

Previously, Brecker *et al.* investigated ^{13}C kinetic isotope effects (KIEs) in the oxidation of cinnamyl alcohol using MnO_2, Dess–Martin periodinane, and Swern oxidation (DMSO/$(COCl)_2$/Et_3N) to gain insight into the reaction mechanism.[20] Comparison of the kinetic isotope of effects revealed the following order MnO_2 > Dess–Martin oxidation ≈ Swern oxidation. The higher ^{13}C KIE using MnO_2 displayed that the C–H bond breaking in the intermediate is irreversible and rate-determining, and the oxidation proceeded *via* energy rich transition state. On the other hand, the lower ^{13}C KIEs observed in Swern oxidation and Dess–Martin oxidation indicated that the intramolecular C–H bond cleavage in these oxidation reaction processes would not be slower to be rate-limiting.

Experimental results in Table 1 clearly shows that the degrees of %D are as follows MnO_2 > PDC > TEMPO ≈ Dess–Martin > SO_3–pyridine/DMSO. It is speculated that higher %D of MnO_2 oxidation and lower %D of SO_3–pyridine/DMSO oxidation would correlate to the ^{13}C KIE data (MnO_2 > Swern oxidation). It is interesting to note that the %D value in Scheme 4 depended on the substrates. The oxidation of propargyl alcohols **4w–4aa** resulted in higher %D than those of the other alcohols. The oxidation of **4w–4aa** needed a longer reaction period to complete the reactions. As mentioned in the previous ^{13}C KIE studies, the rate limiting steps of the MnO_2 oxidation relies on the C–H cleavage step of the reaction intermediate. It is considered that the slower C–H cleavage would provide the higher %D.

3. Conclusions

We have established a facile synthesis of aldehyde-d_1 derivatives by $NaBD_4/MnO_2$ system. The new method is characterized by a high degree of functional group compatibility and a wide range of substrate scope including the synthesis of d-containing unsaturated aldehydes. Aromatic aldehyde-d_1 derivatives such as **2c** and **2g** would be a useful synthetic intermediate for olefination, amination, hydride reduction, Suzuki cross coupling, and Sonogashira coupling reactions.[9e,10c] Substituted acroleins and propynals can be used for Michael addition reaction, cycloaddition reaction, and transition metal catalysed transformations. In this context, $NaBD_4/MnO_2$ system would offer vital opportunity to the synthesis of highly functionalized d-labelled molecules *via* facile preparation of aromatic and unsaturated aldehyde-d_1 **2**. Deuterium-labelled compounds are often needed for the investigation of the mechanisms or determination of the rate-limiting step. The present synthetic method supports the studies from the viewpoint of the facile preparation of aldehyde-d_1 **2** and its derivatives. Further application and mechanism studies are ongoing in our laboratory.

Author contributions

Y. Yasuno and HO are contributed equally. Y. Yasuno, HO, and TS designed the synthetic route. TS wrote the manuscript. HO, Y. Yasuno, and AN prepared ESI.† HO, Y. Yasuno, AN, K. Kumadaki, K. Kitsuwa, KO, YT, and Y. Yamamoto performed syntheses of **2**.

Conflicts of interest

There are no conflicts to declare.

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