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Organocatalytic Nitroaldol Reaction Associated with Deuterium-Labeling

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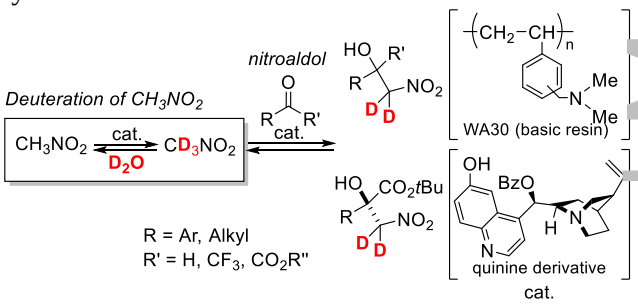
Abstract. A deuterium-labeling reaction of nitroalkanes in deuterium oxide and the subsequent nitroaldol reaction have been accomplished under basic and organocatalytic conditions to provide the deuterium-labeled *β*-nitroalcohols in high yields and high deuterium contents. *β*-Deuterated *β*-nitroalcohols could be smoothly obtained from the reaction of nitroalkanes and various electrophiles using the easily-removal basic resin WA30. Furthermore, the asymmetric nitroaldol reaction using nitromethane and *α*-keto esters as electrophiles in the presence of a quinine-derived organocatalyst in deuterium oxide could provide the desired *β*-deuterated nitroalcohol derivatives with high enantioselectivities.

Keywords: deuterium-labeling; deuterium oxide; enantioselectivity; organocatalysis; nitroaldol reaction

Deuterium-labeled compounds have been utilized in various fields (e.g., the elucidation of metabolic pathways and reaction mechanisms, surrogate compounds for microanalyses of environmental pollutants)[1], and heavy drugs (deuterium-labeled medicines) have been recently spotlighted due to their ability to prolong the duration of drug action based on the isotope effect.[2] Therefore, the novel deuterium incorporation methods into the desired positions of compounds can be powerful tools to provide deuterium-lableled functional materials and their synthetic building blocks. Especially, the use of deuterium oxide (D_2O) as a deuterium source is important from the viewpoint of green sustainable chemistry and cost performance. Catalytic and/or metal-free deuterium-labeling method are also useful as an environmentally friendly method.[3,4] The nitroaldol reaction (Henry reaction)[5] has been widely utilized to synthesize various *β*-nitroalcohol derivatives, which could be transformed into biologically-active compounds,[6] and deuterium-labeled nitromethane (CD_3NO_2) has been used in mechanistic studies to produce the deuterium-incorporated products.[7] While CD_3NO_2 is commercially available, other deuterium-labeled nitroalkane derivatives are expensive or cannot be purchased. Since the nitroaldol reaction accompanied by the deuterium-labeling of CH_3NO_2 has never been developed, we herein report a direct deuteration method of nitroalkanes in D_2O and subsequent nitroaldol reaction with various electrophiles to form the corresponding *β*-deuterated *β*-nitroalcohol derivatives using a heterogeneous basic resin, WA30, as an easily handled organocatalyst, and a quinine-derived organocatalyst for the enantioselective synthesis.

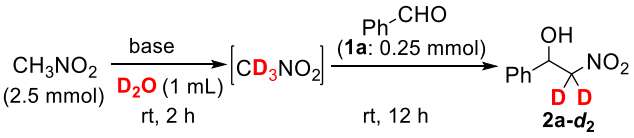


Scheme 1. Organocatalytic nitroaldol reactions with deuterium-labeling.

While the nitroaldol reaction is generally carried out under basic conditions in organic solvents, water (H_2O) has also been used as a solvent in a few reports related to the metal-free nitroaldol reactions.[8] We first investigated the nitroaldol reaction between 0.25 mmol of benzaldehyde (**1a**) and 2.5 mmol of CH_3NO_2 in D_2O (1 mL) under relatively mild basic condi tions (Table 1). After stirring CH_3NO_2 and K_2CO_3 (40 mol%) in D_2O for 2 h at room temperature, **1a** was added to the mixture. After further stirring for 12 h at room temperature, the desired *β*-bisdeuterated *β*-nitroalcohol (**2a-*d*$_2$**) was obtained in 88% yield with 90% D content. Et_3N was also effective to produce **2a-*d*$_2$** with a high D efficiency (entry 2), while the use of quinoline led to the decrease in both the D content and yield (entry 3). On the other hand, the basic resin WA30 (10 mg, 38 wt% toward **1a**, Mitsubishi Chemical Corp.), which is a polystyrene polymer possessing tertiary amine residues on the fundamental skeleton, effectively catalyzed the

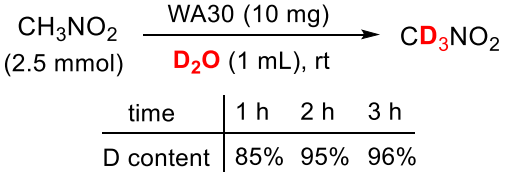
present nitroaldol reaction in association with deuterium-labeling to form **2a-*d*$_2$** with a 96% D content (entry 4), and the increased use of D_2O (2 mL) further improved the reaction efficiency to provide **2a-*d*$_2$** with a nearly quantitative D content (entry 5). A 20-times scale-up test could also be allowed with a high D content and yield (entry 6). It is an important feature that WA30 is easily-eliminated from the reaction media by a simple filtration. Additional investigation results using other bases are detailed in the Supporting Information. WA30 could be reused to give **2a-*d*$_2$** with good deuterium contents, although the slight reduction in the isolated yield was observed (entry 7; the results of the repeated uses (five times) are described in Supporting Information). During the first stirring in the presence of WA30 without **1a**, CH_3NO_2 was effectively deuterated into CD_3NO_2 within 2 h with a quite satisfactory D content (eq. 1).

Table 1. Nitroaldol reactions associated with deuterium-labeling.



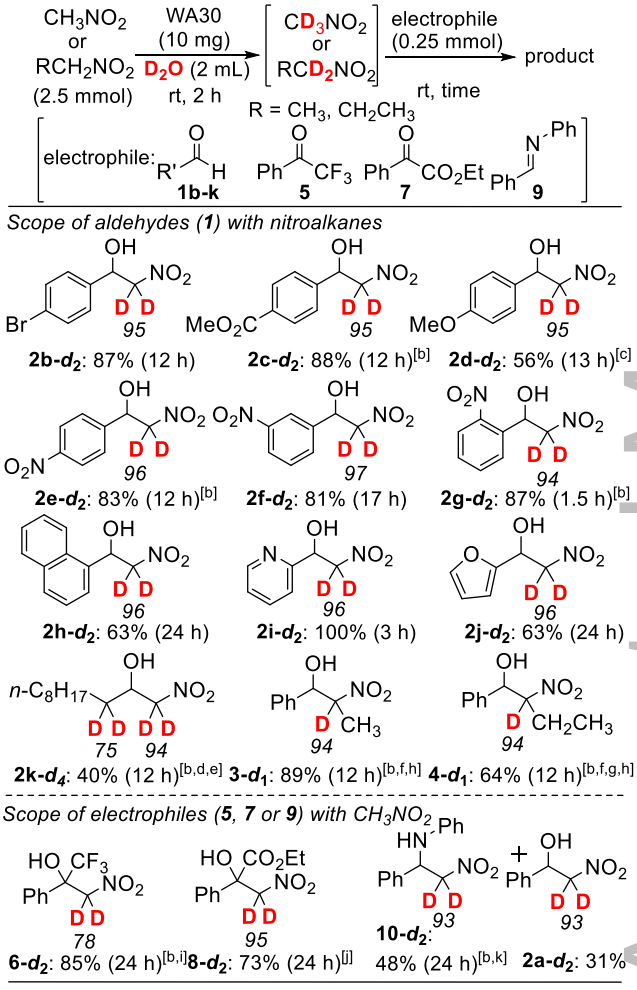
entry	base	D content (%)	yield (%)
1	K_2CO_3 (40 mol%)	90	88
2	Et_3N (40 mol%)	86	100
3	quinoline (40 mol%)	32	22
4	WA30 (10 mg)	96	88
5[a]	WA30 (10 mg)	99	75
6[b]	WA30	96	84
7	Reused WA30	93	78

[a] 2 mL of D_2O was used.
[b] 5 mmol of **1a**, 200 mg of WA30 and 20 mL of D_2O were used.



Various electrophiles and nitroalkane derivatives were next investigated (Table 2). 4-Bromo-, 4-methoxycarbonyl-, 4-methoxy-, 4-nitro-, 3-nitro- and 2-nitro-benzaldehyde derivatives (**1b**–**1g**) were all smoothly transformed into the corresponding *β*-bisdeuterated *β*-nitroalcohols (**2b-*d*$_2$**–**2g-*d*$_2$**) based on the coupling of the *in situ*-generated CD_3NO_2 with excellent D efficiencies and good to high yields. Naphthylaldehyde (**1h**) and heteroaromatic aldehydes (**1i** and **1j**) were also good substrates. Decanal was converted to the tetradeuterated nitroalcohol (**2k-*d*$_4$**) via the initial WA30-catalyzed *α*-deuteration of decanal and the following nitroaldol reaction between CD_3NO_2 and the partially *α*-deuterated decanal. Nitroethane ($EtNO_2$) and nitropropane (*n*-$PrNO_2$) were also available for the present reaction, and the corresponding mono-deuterated products (**3-*d*$_1$** and **4-*d*$_1$**) were obtained as diastereomixtures. Trifluoromethylacetophenone (**5**) and ethyl benzoylformate (**7**) were also effectively reacted with the *in situ*-generated CD_3NO_2 to give the *β*-bisdeuterated *β*-nitroalcohols (**6-*d*$_2$** and **8-*d*$_2$**) with good D efficiencies. The *β*-bisdeuterated *β*-nitroamine derivative (**10-*d*$_2$**) could be obtained from (*E*)-*N*-benzylideneaniline (**9**) in a moderate yield along with generation of the *β*-bisdeuterated *β*-nitroalcohol (**2a-*d*$_2$**) via the hydrolyzed benzaldehyde (**1a**).

Table 2. Scope of substrates under WA30-catalyzed conditions.[a]



[a] The reaction was carried out using CH_3NO_2 and an aldehyde (**1**) unless otherwise noted.
[b] 1 mL of D_2O was used.
[c] K_2CO_3 (20 mol%) was added.
[d] At 50 °C for the second step.
[e] 20 mg of WA30 was used.
[f] $EtNO_2$ was used instead of CH_3NO_2.
[g] *n*-$PrNO_2$ was used instead of CH_3NO_2. The first step was for 24 h.

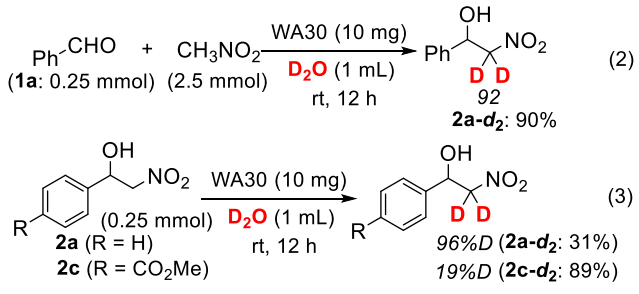
[h] The product was obtained as a diastereomixture.

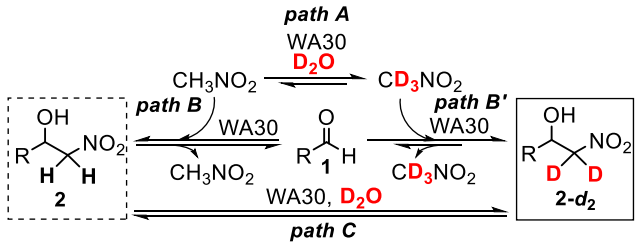
[i] **5** was used as the substrate.

[j] **7** was used as the substrate.

[k] **9** was used as the substrate.

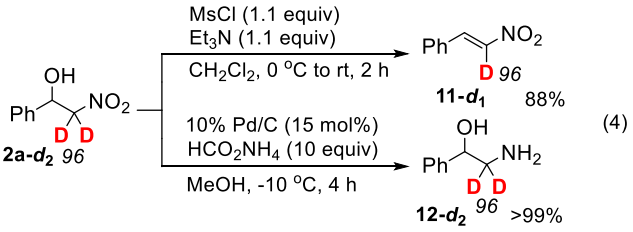
The stepwise addition of CH_3NO_2 and benzaldehyde (**1a**) shown in Table 1 was not essential, and the *β*-bisdeuterated *β*-nitroalcohol (**2a-*d*$_2$**) could be obtained with satisfactory 92% D contents by the mixed use of CH_3NO_2 and **1a** in D_2O from the outset of the reaction (eq. 2). Furthermore, the WA30-catalyzed direct deuteration of unlabeled *β*-nitroalcohols (**2a** or **2c**) produce the only a 31% yield of **2a-*d*$_2$** or only a 19% D efficiency of **2c-*d*$_2$** (eq. 3). **2a** preferentially underwent the retroaldol reaction to give benzaldehyde, which resulted in low yield of **2a-*d*$_2$**. Meanwhile, the reason for the lower deuterium efficiency of **2c** was unclear. Three equilibrium reactions in the nitoroaldol reaction associated with deuterium labeling, such as the deuteration (H-D exchange reaction) of CH_3NO_2 *vs.* the reverse D-H exchange reaction (path A), nitroaldol *vs.* retroaldol reactions between **1** and **2** (path B and B') and the direct H-D exchange *vs.* D-H exchange reactions of **2** (path C) can be proposed (Scheme 2). The excess use of D_2O toward CH_3NO_2 facilitates the generation of CD_3NO_2 which is also sufficiently generated to promote the subsequent nitroaldol reaction of **1** into the deuterium-labeled nitroalcohol product (**2-*d*$_2$**). Additionally, **2-*d*$_2$** can be directly obtained from the non-labeled **2**. The stability of the C-D bonds based on the isotope effect also contributes to preferentially generate the deuteration processes (paths A and C). Consequently, the deuterium-labeled nitroalcohol product (**2-*d*$_2$**) with high deuterium contents is available.





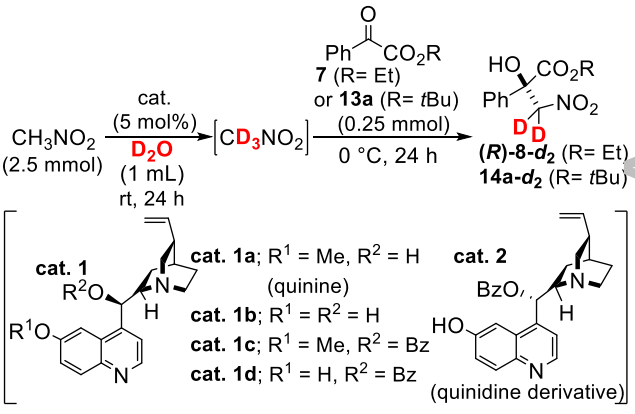
Scheme 2. Proposed reaction mechanism of WA30-catalyzed deuteration of CH_3NO_2 and subsequent nitroaldol reaction.

The generated deuterium-labeled product **2a-*d*$_2$** could undergo a further transformation by elimination of the hydroxy group using the combination of mesyl chloride (MsCl) and Et_3N into the corresponding *β*-nitrostyrene (**11-*d*$_1$**) and the Pd/C-catalyzed hydrogen transfer reaction using ammonium formate as a hydrogen source into the *β*-aminoalcohol (**12-*d*$_2$**) with retention of the D contents (eq. 4).



The asymmetric nitroaldol reaction accompanied by the deuterium-labeling using a chiral basic organocatalyst in D_2O was also investigated (Table 3). The enantioselective nitroaldol reactions without the deuterium-labeling step in aqueous media have been accomplished using transition metal-based chiral catalysts.[9] Although the organocatalytic nitroaldol reactions using cinchona alkaloid derivatives were also reported in the literature, organic solvents (CH_2Cl_2 and THF) were always required.[10] We chose quinine and quinidine derivatives bearing tertiary amine and quinoline moieties within the molecule, which facilitates the desirable asymmetric nitroaldol reaction associated with the deuterium-labeling process in D_2O as shown in Table 3. While quinine (**cat. 1a**) and its derivatives (**cat. 1b** and **cat 1c**) were inefficient (entries 1-3), the **cat. 1d** [R^1 = H, R^2 = benzoyl (Bz)]-catalyzed nitroaldol reaction of CH_3NO_2 and ethyl benzoylformate (**7**) in D_2O could efficiently proceed to form the desired product **(*R*)-8-*d*$_2$**[11] in high yield, D content and ee (entry 4).[12] The use of the benzoyl quinidine derivative (**cat. 2**) also effectively provided **(*S*)-8-*d*$_2$** (entry 5). The *tertiary*-butyl benzoylformate (**13a**) was a more suitable substrate to improve the enantioselectivity to produce **14a-*d*$_2$** in 94% ee (entry 6).

Table 3. Application to asymmetric reaction using benzoylformate (**7** or **13a**).



entry	catalyst	R	D content (%)	yield (%)	ee
1	**cat. 1a**	Et	89	98	12

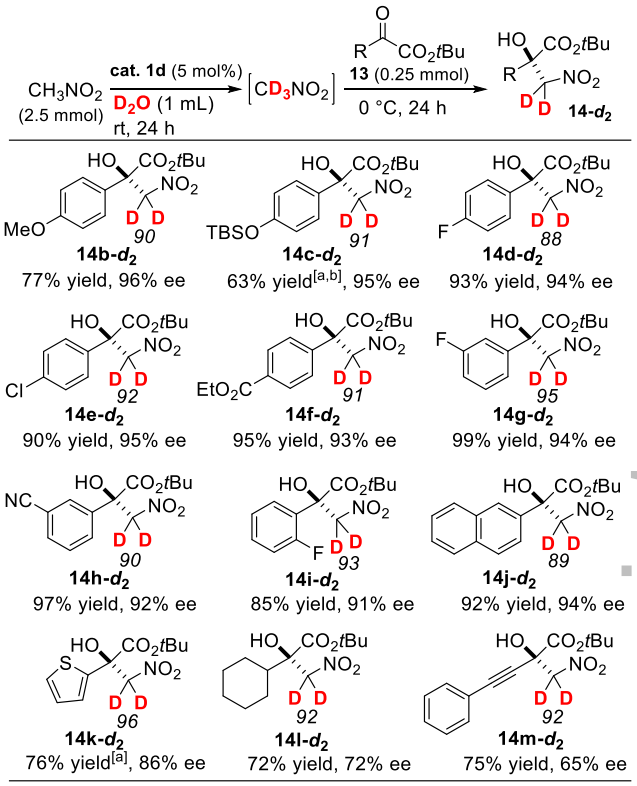
10.1002/adsc.201701224

2	**cat. 1b**	Et	84	93	66
3	**cat. 1c**	Et	93	7	35
4	**cat. 1d**	Et	94	98	90
5	**cat. 2**	Et	91	94	90[a]
6	**cat. 1d**	*t*Bu	93	93	94

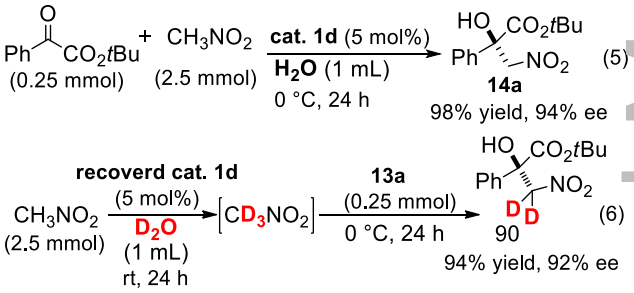
[a] **(*S*)-8-*d*$_2$** was obtained as the principal product.

tertiary-Butyl benzoylformate derivatives (**13b**–**13i**) bearing various functionalities, such as methoxy, siloxy, fluoro, ethoxycarbonyl and nitrile groups, on the aromatic ring were efficiently and enantioselectively reacted with the *in situ*-generated CD_3NO_2 in the presence of **cat. 1d** to give the corresponding chiral *β*-bisdeuterated *β*-nitroalcohol products (**14b-*d*$_2$**–**14i-*d*$_2$**) with high D contents and excellent ee values (Table 4). **13j** and **13k** bearing naphthalene- (**13j**) and thiophene- (**13k**) rings also underwent the asymmetric nitroaldol reaction with deuterium labeling to provide the desired products (**14j-*d*$_2$** and **14k-*d*$_2$**) in good to excellent enantioselectivities. Although the reaction of the cyclohexyl (**13l**) and phenylalkynyl (**13m**) derivatives also stereoselectively proceeded, their enantioselectivities were slightly decreased.[13] Because the **cat. 1d**-catalyzed reaction of **13a** in H_2O instead of D_2O gave the non-labeled chiral *β*-nitroalcohol product (**14a**) with an excellent ee (eq. 5), the present metal-free methodology is also useful as a simple asymmetric reaction without the deuterium-labeling process from view point of green sustainable chemistry. Furhtermore, **cat. 1d** recovered after the reaction could be reused without decreasing the catalytic activity (eq. 6).

Table 4. Organocatalytic and asymmetric nitroaldol reaction associated with deuterium labeling.



[a] The second step was for 48 h.
[b] 19% of the substrate was recovered.



In conclusion, we have developed the efficient synthetic method to construct *β*-deuterated *β*-nitroalcohols by the base-catalyzed deuteration of nitroalkanes in D_2O and the consecutive nitroaldol reaction in a one-pot manner. The present reaction could be heterogeneously catalyzed by the easily-eliminable WA30 to give the corresponding *β*-deuterated *β*-nitroalcohol derivatives (**2**–**4**, **6**, **8**). Furthermore, a quinine-derived organocatalyst (**cat. 1d**) allowed the highly enantioselective reaction of *α* keto ester derivatives (**7** and **13**) to efficiently provide the desired chiral deuterium-labeled products (**8** and **14**). The present unprecedented methodology can easily provide various *β*-deuterated *β*-nitroalcohol products, as deuterium-labeled synthetic building blocks.

Experimental Section

Experimental Details WA30-catalyzed reaction: A solution of a nitroalkane (2.5 mmol, 134 μL) and WA30 (10 mg) in D_2O (1 mL) was stirred at rt for 2 h. An aldehyde (1: 0.25

mmol) was added to the reaction mixture and stirred for 12 h. The reaction mixture was filtered and the filtrate was extracted with Et_2O (5 mL x 2). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica-gel column chromatography to give the β-deuterated β-nitroalcohol 2-d_x.

Asymmetric reaction: A solution of CH_3NO_2 (2.5 mmol, 134 μL) and **cat. 1d** (5 mol%) in D_2O (1 mL) was stirred at rt for 24 h. An acylformate (**7** or **13**) (0.25 mmol) was added to the reaction mixture at 0 °C and stirred for 24 h. The reaction mixture was directly purified by silica-gel column chromatography to produce **14-*d*$_2$**.

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[11] The absolute configuration of **(*R*)-** or **(S)-8-*d*$_2$** was determined according to the chiral HPLC data of the unlabeled compounds **(*R*)-** and **(*S*)-8** shown in reference 10d.

[12] The results using various substrates [e.g., benzaldehyde (**1a**), α,α,α-trifluoromethylacetophenone **5** and acylformates (**13**)], and various organocatalysts are described in the Supporting Information.

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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