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N-Heterocyclic Carbene Catalyzed Deuteration of Aldehydes in D_2O

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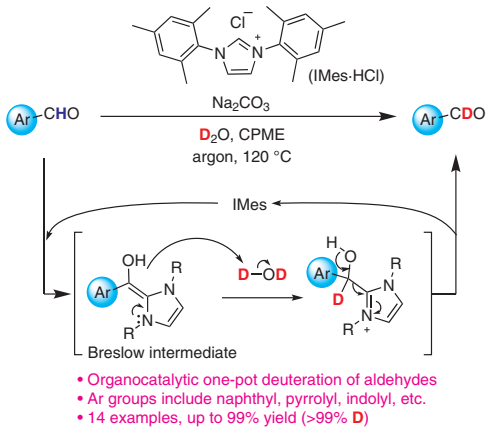

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Abstract An N-heterocyclic carbene (NHC)-catalyzed direct deuteration of aldehydes in a mixed solvent of deuterium oxide (D_2O) and cyclopentyl methyl ether was established. The present deuteration is possibly initiated by the formation of a Breslow intermediate from the aldehyde and the NHC, with subsequent trapping by D_2O providing the monodeuterated aldehyde.

Key words deuteration, aldehydes, N-heterocyclic carbenes, organocatalysis

Deuterium (^{2}H, D) is a stable isotope of hydrogen (^{1}H), and deuterium-labeled compounds are widely used in various scientific fields related to microanalysis, elucidation of organic reaction mechanisms, heavy drugs, and isotopic contrast, among others.[1] Consequently, many direct approaches have been developed for the synthesis of deuterium-labeled materials from mother substrates.[2] Because aldehydes are useful precursors as electrophiles that can be transformed into various functional groups, deuterium-labeled aldehydes (aldehydes-d_1) can serve as valuable synthons for syntheses of deuterium-labeled target molecules. In conventional methods, aldehydes-d_1 are constructed by a stepwise process, such as the reduction of esters to deuterium-labeled alcohols by using an expensive deuteride source such as $LiAlD_4$, and subsequent oxidation to give the aldehyde-d_1.[3] Alternatively, an umpolung reaction via cyanohydrin intermediates derived from aldehydes can also be used to prepare aldehydes-d_1.[4] Treatment of the cyanohydrin intermediates with a strong base such as BuLi and subsequent quenching by with D_2O gives a monodeuterated cyanohydrin intermediates that can be hydrolyzed to form the aldehydes-d_1. There have been recent reports of platinum-group-metal-catalyzed syntheses of derivatives of aldehydes-d_1 from aryl halides[5] or benzoic acids[6] by using D_2O as the least expensive source of deuterium among the various labeling agents that are available. Although the direct deuteration of aromatic aldehyde can be accomplished by using a homogeneous Ir catalyst under atmospheric D_2 gas[7] or a Ru catalyst in D_2O,[8] the deuteration efficiencies are low to moderate and concomitant deuteration of the aromatic moiety cannot be suppressed. We have investigated platinum-group-metal-catalyzed polydeuterations of various compounds,[2b,c,9] as well as organocatalyzed deuterium labeling of alkynes[10a,b] or nitromethane.[10c] Furthermore, an N-heterocyclic carbene (NHC)-catalyzed direct deuteration of aromatic aldehydes to aldehydes-d_1 has recently been studied in our laboratory (Scheme 1). NHC is known to react with aldehydes **1** to give the corresponding Breslow intermediates **A**, which couple with another molecule of aldehyde **1** to give a benzoin product.[11] If the Breslow intermediate **A** could be trapped by D_2O, the corresponding monodeuterated aldehyde **1-*d*$_1$** would be reliably obtained without deuteration of the aromatic ring of **1**. Unfortunately, an NHC-catalyzed deuteration of aldehydes by D_2O involving a similar concept to our present results was published in October 2019.[12]

4-Methoxybenzaldehyde (**1a**: 0.2 mmol) was treated with D_2O (1 mL) in the presence of 1,3-dimesitylimidazolium chloride (IMes·HCl; **3**, 20 mol%) and Na_2CO_3 at 120 °C for six hours to give the desired monodeuterated aldehyde **1a-*d*$_1$** in 74% yield with 84% D content; this was accompanied by the formation of 15% of the benzoin derivative **2a-*d*$_1$** (Table 1, entry 1). Whereas the use *N*,*N*-dimethylacetamide (DMA), *N*,*N*-dimethylformamide (DMF), or 1,4-dioxane as a cosolvent suppressed both the desired deuteration and the

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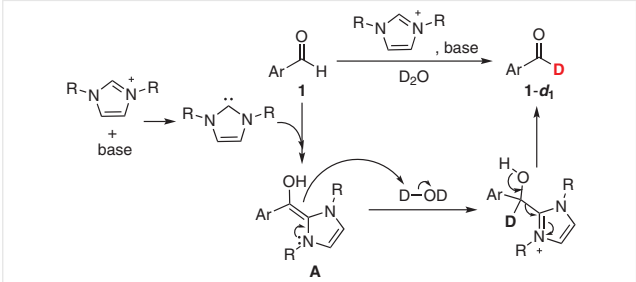
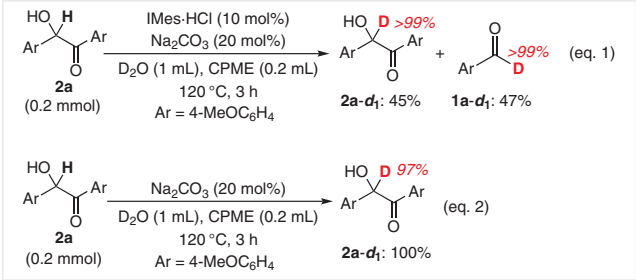


Scheme 1 The concept of direct deuteration of aldehydes by using an N-heterocyclic carbene

benzoin condensation (entries 2–4), tetrahydrofuran (THF), toluene, and cyclopentyl methyl ether (CPME) were efficient cosolvents, giving **1a-*d*$_1$** in moderate yields with quantitative D content (entries 5–7). CPME was chosen as the preferred solvent because of its excellent stability against oxidation (peroxide formation), which makes it suitable for use in process chemistry.[13] The deuteration was completed within two hours when CPME was used as the cosolvent (entry 8). Deuterations at lower temperatures (80 °C or 25 °C) hardly proceeded (entries 9 and 10). When the catalyst loading was reduced from 20 mol% to 10 mol%, **1a-*d*$_1$** was obtained in moderate yield with quantitative D content (entry 11).

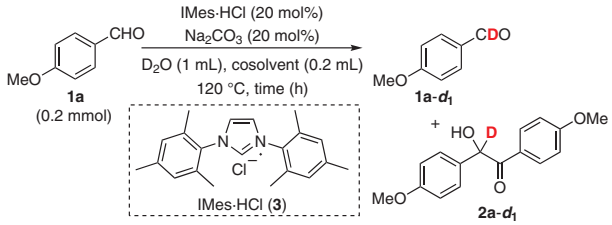
During the deuteration of **1a**, the benzoin byproduct **2a-*d*$_1$** was also deuterated quantitatively. The unlabeled benzoin derivative **2a** was also directly deuterated in the presence of IMes and D_2O with generation of the deuterated aldehyde **1a-*d*$_1$**, as shown in Scheme 2 (eq. 1). These results indicated that the present reaction is an equilibrium that depends on the substrate (see also Table 3 below). Additionally, the deuteration of **2a** effectively proceeded in basic D_2O to give **2a-*d*$_1$** in nearly quantitative yield and D content through a base-catalyzed keto–enol tautomerism (Scheme 2, eq. 2).



Scheme 2

Next, we examined the effects of various catalysts (Table 2).1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) and 1,3-bis(diphenylmethyl)imidazol-2-ylidene, derived from catalysts **4** and **7**, respectively, were also effective in providing **1a-*d*$_1$** in moderate yields and with high D contents (Table 2, entries 2 and 7), whereas other imidazolium salts **5**, **6** and **8** and thiazolium salts **9**–**11** were less

Table 1 Effects of the Cosolvent, Temperature, and Catalyst Loading



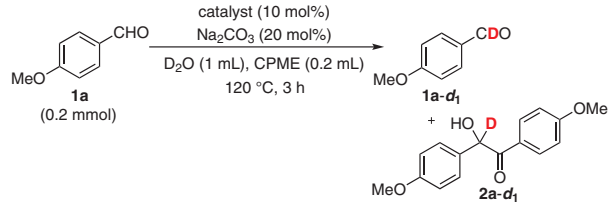
Entry	Cosolvent	Time (h)	Yield (%)		D content of **1a-*d*$_1$** (%)
			1a-*d*$_1$	**2a-*d*$_1$**[a]	
1	–	6	74	15	84
2	DMA	6	100	trace	7
3	DMF	6	95	trace	10
4	1,4-dioxane	6	91	trace	47
5	THF	6	45	49	>99
6	toluene	6	50	50	>99
7	CPME	6	50	50	>99
8	CPME	2	60	40	>99
9[b]	CPME	2	91	7	14
10[c]	CPME	2	100	0	0
11[d]	CPME	3	59 (58)[e]	41 (38)[e]	>99

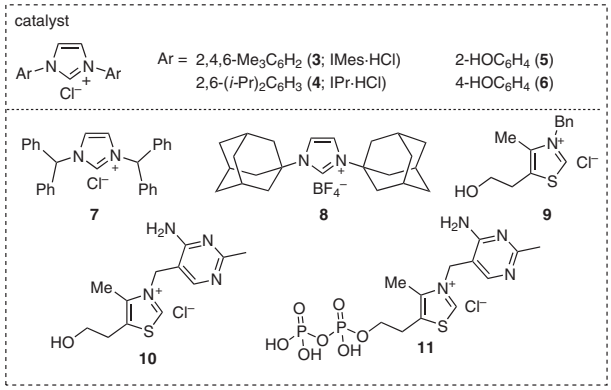
[a] A 100% yield of the benzoin product **2a-*d*$_1$** means that 0.1 mmol of **2a-*d*$_1$** was obtained. Therefore, a 50% yield indicates the isolation of 0.05 mmol of **2a-*d*$_1$**.
[b] At 80 ℃.
[c] At 25 ℃.
[d] IMes·HCl (10 mol%) was used.
[e] Isolated yield.

reactive as NHC precursors (entries 3, 4, and 6–9). As a result of our screening of various catalysts, IMes was chosen as the optimal organocatalyst for the direct deuteration of aldehydes (entry 1).

We then examined the scope of the reaction with respect to the aldehyde (Table 3).[14,15] 2,4-Dimethoxybenzaldehyde (**1b**), 2,6-dimethoxybenzaldehyde (**1c**), and 4-methoxy-1-naphthaldehyde (**1d**) were efficiently deuterated in excellent yields and with excellent D contents (Table 3, entries 1–3). The deuteration of unsubstituted 1-naphthaldehyde (**1e**) and 4-(benzyloxy)benzaldehyde (**1f**) gave moderate yields of the corresponding quantitatively deuterated aldehydes **1e-*d*$_1$** and **1f-*d*$_1$**, together with benzoin byproducts (entries 4 and 5). 1-Benzyl-1*H*-indole-3-carbaldehyde (**1g**) and pyrrole-2-carbaldehyde (**1h**) were also efficiently deuterated (entries 6 and 7), whereas 1-benzyl-1*H*-pyrrole-2-carbaldehyde (**1i**) gave the deuterated derivative in moderate yield and D content (entry 8). 4-Bromobenzaldehyde (**1j**), 2-bromobenzaldehyde (**1k**), 3-methoxybenzaldehyde (**1l**), and 2-methoxybenzaldehyde (**1m**) gave the corresponding products with high D contents but in low to moderate yields (entries 9–12). 4-(Dimethylamino)benzaldehyde (**1n**) was also moderately deuterated (entry 13). Although deuteration efficiencies and yields were strongly

Table 2 Effects of Various Catalysts



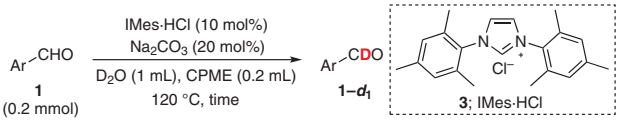


Entry	Catalyst	Yield (%)		D content of **1a-*d*$_1$** (%)
		1a-*d*$_1$	**2a-*d*$_1$**	
1	**3**	59	41	>99
2	**4**	41	47	78
3	**5**	95	–	0
4	**6**	99	–	0
5	**7**	46	50	>99
6	**8**	97	–	0
7	**9**	87	–	11
8	**10**	97	–	2
9	**11**	99	–	4

influenced by the electronic and steric properties of the substrate, detailed tendencies in the direct deuteration remain unclear.

In conclusion, we have established a method for the direct deuteration of aldehydes by using an NHC catalyst in a mixed solvent of D_2O and CPME. The present method is reliable for the monodeuteration of aldehydes. D_2O is the least expensive deuterium source, and CPME is a process-chemistry-friendly solvent. In comparison with the results reported in a recent publication,[12] the range of substrates that we examined was somewhat different, and the deuteration of the benzoin byproduct was also accomplished. Our alternative method is also useful for the construction of deuterated target materials by using the resulting monodeuterated aldehydes.

Table 3 Scope of Substrates



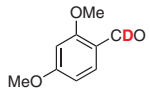
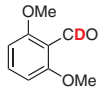
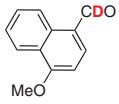
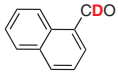
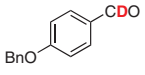
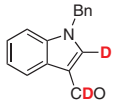
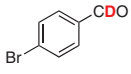
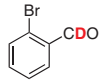
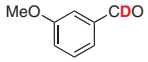
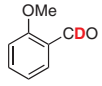
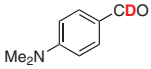
Entry	Product	Time	Yield (%)	D content of aldehyde (%)
1	 **1b-*d*$_1$**	3 h	99	90
2	 **1c-*d*$_1$**	3 h	91	>99
3	 **1d-*d*$_1$**	3 h	98	94
4	 **1e-*d*$_1$**	3 h	68	>99
5	 **1f-*d*$_1$**	3 h	51 (60)[a]	>99
6	 **1g-*d*$_2$**	24 h	70	91[b]
7	 **1h-*d*$_1$**	3 h	86	>99
8	 **1i-*d*$_1$**	24 h	79	65
9	 **1j-*d*$_1$**	5 min	19	>99
10	 **1k-*d*$_1$**	5 min	52	90

Table 3 (continued)

Entry	Product	Time	Yield (%)	D content of aldehyde (%)
11	 **1l-d_1**	3 h	21	>99
12	 **1m-d_1**	3 h	55	>99
13	 **1n-d_1**	24 h	81	57

[a] Isolated yield.
[b] There was 37% incorporation of deuterium at the 2-position of **1g**.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707993.

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(14) **Monodeuterated Aldehydes 1a-d_1 to 1n-d_1; General Procedure**
An 18 mL test tube was charged with the appropriate aldehyde (0.2 mmol), IMes·HCl (6.8 mg, 0.02 mmol), Na_2CO_3 (4.2 mg, 0.04 mmol), CPME (0.2 mL), and D_2O (1.0 mL). The tube was then sealed with a septum and the gas inside the tube was immediately replaced with Ar. The mixture was then heated at 120 °C for the appropriate time (Table 3), then extracted with EtOAc. The organic layers were dried ($MgSO_4$) and concentrated in vacuo. If necessary, the residue was purified by column chromatography (silica gel).
4-Methoxybenzaldehyde-d_1 (**1a-d_1**): Yield: 15.8 mg (58%; 99% D incorporation). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.88 (s, 0.01 H), 7.84 (d, *J* = 8.2 Hz, 2 H), 7.00 (d, *J* = 8.2 Hz, 2 H), 3.89 (s, 3 H). ^{2}H NMR (77 MHz, $CHCl_3$): δ = 9.91 (br s).

(15) Because of the volatility of the aldehyde products, yields were determined by ^{1}H NMR with CH_2Br_2 as an internal standard, unless otherwise noted.