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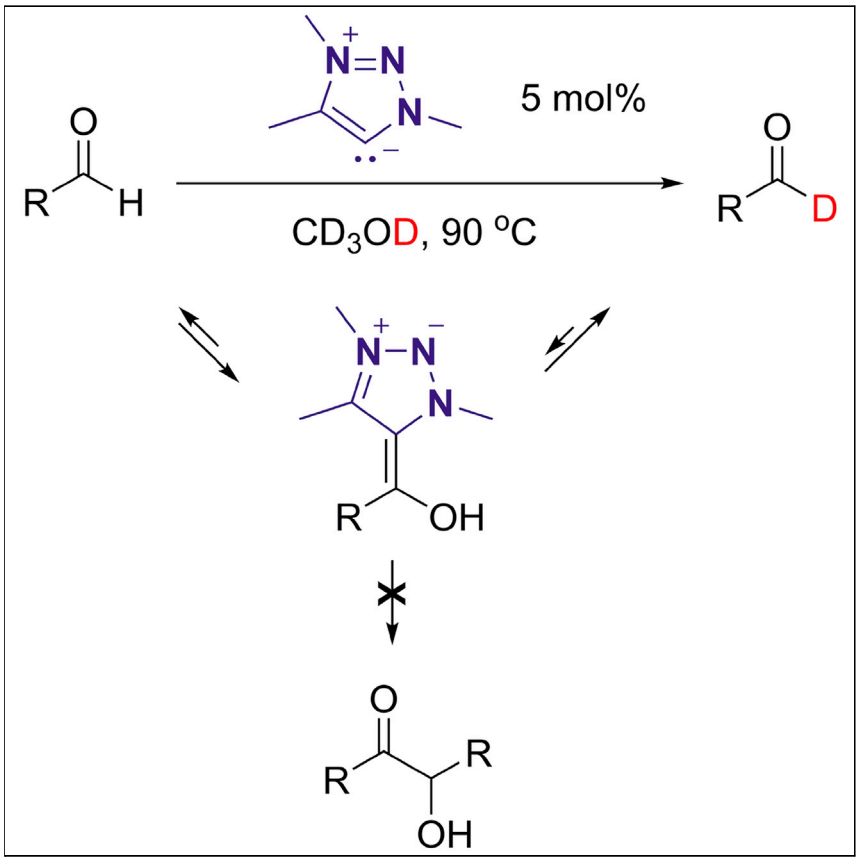
Mesoionic Carbene (MIC)-Catalyzed H/D Exchange at Formyl Groups



The formation of Breslow intermediates in the reaction of 1,2,3-triazolylidenes (mesoionic carbenes) with aldehydes is reversible. The benzoin condensation is inhibited in deuterated methanol, allowing for H/D exchange at formyl groups.

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HIGHLIGHTS

A metal-free catalyzed H/D exchange at formyl groups is described

The formation of Breslow intermediates is reversible with 1,2,3-triazolylidenes (MICs)

Interrupted benzoin condensation in deuterated methanol

Broad scope of applications for aldehydes and even aldimines

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Mesoionic Carbene (MIC)-Catalyzed H/D Exchange at Formyl Groups

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SUMMARY

H/D exchange at formyl groups is the most direct approach for the synthesis of deuterated aldehydes. Platinum-group metal complexes have been employed to catalyze this transformation, with significant substrate scope limitations. Although N-heterocyclic carbenes can also activate the C–H bond of aldehydes through the formation of Breslow intermediates, benzoin condensation and other C–C-bond-forming pathways have so far outpaced synthetically useful H/D exchange. Investigation of the reaction of aldehydes with 1,2,3-triazolylidenes has revealed the reversible formation of Breslow intermediates and the inhibition of the condensation steps in methanol solvent. 1,2,3-Triazolylidenes catalyze the H/D exchange of aryl, alkenyl, and alkyl aldehydes in high yields and deuterium incorporation levels using deuterated methanol as an affordable D source. The unique properties of these mesoionic carbenes (MICs) enable a streamlined preparation of deuterated synthetic intermediates and pharmacophores that are highly valuable as mechanistic and metabolic probes.

INTRODUCTION

Deuterium-labeled chemicals find widespread uses across multiple scientific fields. In materials chemistry, deuteration of aromatic phosphors decreases their non-radiative deactivation rates, resulting in room-temperature phosphorescent compounds with higher quantum yields.[1–4] The reduced lability of C–D bonds over C–H bonds, known as a kinetic isotope effect (KIE), is widely used in pharmaceutical sciences to both study and alter the metabolism and pharmacokinetics of drugs.[5–8] In organic chemistry, KIE experiments are privileged tools for the study of reaction mechanisms,[9,10] and the strategic use of KIEs has enabled the landmark syntheses of a growing number of complex natural products.[11–15] Because of their versatility as organic building blocks, deuterated aldehydes (R–CDO) are frequently employed in these experiments and as intermediates for the synthesis of other deuterated compounds.[16–21] A number of approaches, such as the reduction of carboxylic acid derivatives[22–25] (Figure 1A) and the carbonylation of aryl halides[26] (Figure 1B), have been reported for the preparation of deuterated aldehydes. However, these reactions not only use expensive transition metal catalysts and/or deuterated reductants, but they also usually require multiple steps. Consequently, direct formyl H/D exchange reactions are highly preferable.[27–29] Recently, Kerr and co-workers reported a selective deuteration of aromatic aldehydes (Figure 1C), which involves the activation of formyl C–H bonds by an iridium catalyst and isotope exchange with D_2.[30] Newman and co-workers developed a ruthenium-catalyzed formyl H/D exchange reaction of aromatic aldehydes with D_2O able to achieve up to 84% deuteration (Figure 1C).[31] Nevertheless, these H/D exchange reactions still rely on noble-metal catalysts, and their substrate scope remains mostly limited to aromatic aldehydes.

The Bigger Picture

Incorporation of deuterium atoms in organic molecules is an important tool for the identification and understanding of chemical and biological processes. Deuterium labeling of organic and inorganic molecules allows for simple and direct incorporation of a useful analytical probe while keeping their structure, physical properties, and biological activity intact. Deuterium-labeled compounds can be readily identified using conventional techniques such as NMR spectroscopy, mass spectrometry, and even elastic neutron scattering. Such methods are widely popular in life sciences where they provide high levels of insight into various processes and also offer a widening range of applications in several fields of chemistry. Herein, we report the cheap and efficient metal-free catalytic synthesis of deuterium-labeled carbonyls and related compounds.

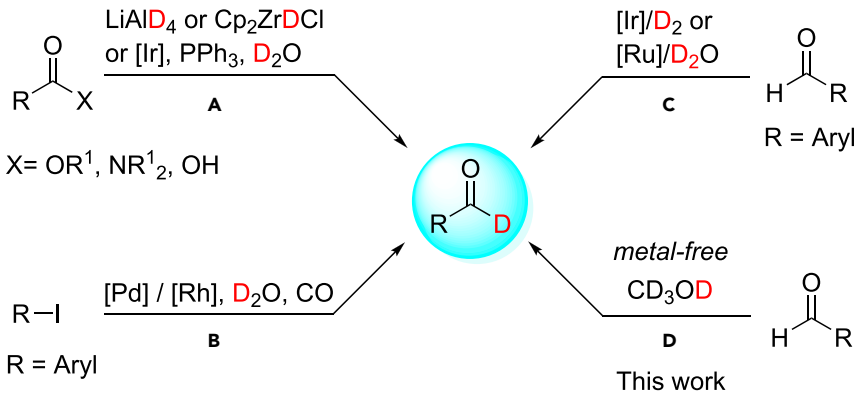

Figure 1. Synthetic Methods to Formyl-Deuterated Aldehydes

(A) Reduction of carboxylic acid derivatives with a deuterated reductant and/or a transition metal.

(B) Carbonylation of aryl halides.

(C) Transition-metal-catalyzed H/D exchange reactions of aldehydes.

(D) Our approach to H/D exchange reactions of aldehydes with a metal-free catalyst.

It is well known that the C–H bond of aldehydes can be activated by N-heterocyclic carbenes (NHCs) through nucleophilic addition and the subsequent formation of a Breslow intermediate.[32–35] To apply this mode of activation to the preparation of deuterated aldehydes, the reversibility of this reaction must be ensured, and undesired C–C-bond-forming pathways must be blocked. Although the NHC-catalyzed benzoin condensation reaction is reversible,[36,37] recent advances in NHC-catalyzed reactions have instead featured catalytic cycles where the Breslow intermediate reacts rapidly once generated, making its formation effectively irreversible.[37–42] Investigating the redox esterification of cinnamaldehyde to hydrocinnamate derivatives, Bode and co-workers observed a competing H/D exchange reaction when aldehydes were reacted with CH_3OD in the presence of catalytic amounts of 1,2,4-triazolium and triethylamine.[43,44] This H/D exchange reaction was not, however, suitable for the preparation of deuterated aldehydes, given its low yield and weak deuterium incorporation. Out competition by the benzoin condensation and other undesired pathways, which is responsible for these poor outcomes, has thus far only been circumvented through the use of >1 equiv catalyst in combination with phase isolation techniques, as previously reported by Bergbreiter, Newcomb, and co-workers.[45]

Here, we report a catalytic metal-free direct formyl H/D exchange reaction that is both highly selective and broad in scope (Figure 1D).

RESULTS AND DISCUSSION

Having in hand a variety of stable metal-free 1,2,3-triazolylidenes,[46–48] a type of mesoionic carbene (MIC) that has rarely been used as organocatalysts,[49] we were drawn to the observation that the MIC-catalyzed benzoin condensation was strongly impacted by the polarity of solvents. In toluene solution, treatment of aldehyde **1a** with 5 mol % of MIC $\mathbf{A_1}$ cleanly afforded the benzoin **2a**, which was isolated in 91% yield. However, under the same experimental conditions, the yield of **2a** decreased to 54% and <5% in tetrahydrofuran (THF) and methanol, respectively (Figure 2).

In an attempt to understand these results, we carried out stoichiometric reactions mimicking the individual steps of the benzoin condensation mechanism. Treatment of MIC $\mathbf{A_1}$ in THF with 1 equiv of aldehyde **1a** afforded a dark-green solution for

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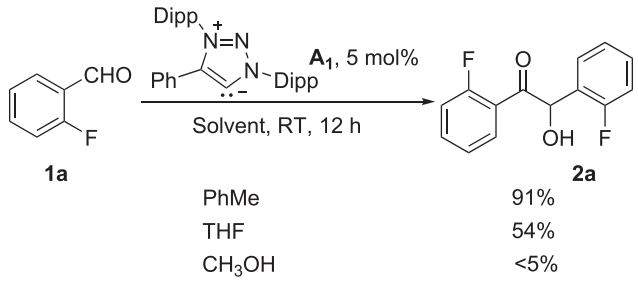


Figure 2. Influence of the Solvent on the MIC A_1-Catalyzed Benzoin Condensation

Reaction conditions: **1a** (0.1 mmol) and solvent (3 mL) at room temperature (RT) for 12 h. The yield of **2a** in PhMe, THF, and CH_3OH was determined by ^1H NMR with CH_2Br_2 as internal standard.

which the characteristic ^1H and ^{19}F NMR signals of both reactants were not present. The ^{19}F NMR spectrum showed two new signals at −111.8 and −118.6 ppm (2:1 ratio), but the complexity of the ^1H and ^{13}C NMR spectra did not allow for unequivocal structure determination. However, the addition of trifluoroacetic acid (TFA) to this THF solution afforded salt **3a**, which was unambiguously characterized by X-ray diffraction analysis (Figure 3). Moreover, addition of TFA-d_1 instead of TFA afforded **3a(D)** and **3a(D)′** in a 1:4 ratio. These results as a whole suggest that the dark-green solution is composed of the Breslow intermediate **B** and carbene-aldehyde adduct **C**. This hypothesis is reinforced by the formation of the same dark-green solution when **3a** was treated with potassium hexamethyldisilazide (KHMDS) in THF. Lastly, DFT calculations suggest that, unlike for NHCs, the MIC-derived Breslow intermediate **B** and carbene-aldehyde adduct **C** are very close in energy, which supports their possible co-existence in solution (see Supplemental Information).

Assignment of the mixture constituents as the Breslow intermediate **B** and carbene-aldehyde adduct **C** was further supported by an independent synthesis of the dark-green O-methylated analog **B′**, whose structure was confirmed by an X-ray diffraction study (Figure 3, part f). By comparison with the previously reported solid-state structures of O-methylated Breslow intermediates derived from imidazolylidenes, imidazolylinylidenes, thiazolylidenes, and 1,2,4-triazolylidenes,[34,50] **B′** features an elongated exocyclic CC bond (138.6 pm) that is considerably twisted out of planarity (∠NCCO: 20.84°). These measurements are consistent with a highly polarized C=C double bond, as confirmed by a computed proton affinity that is ca. 8 kcal/mol higher for Breslow intermediates derived from MICs than for other families of carbenes. Further calculations indicate that the differences in enthalpy between the free aldehyde and MIC pair, the initial aldehyde adduct, and the Breslow intermediate are of ca. 2 kcal/mol, whereas for thiazolylidenes and 1,2,4-triazolylidenes the corresponding enthalpy gaps are far greater (5–21 kcal/mol) (see Supplemental Information). We postulate that these features promote the reversible addition onto aldehydes and formation of Breslow intermediates with MICs.

Interestingly, the quenching of **B**/**C** was impacted by the acidity of proton donors. When NH_4PF_6, an acid weaker than TFA, was employed, **3a** was not observed. Instead, A_1H, the conjugate acid of 1,2,3-triazolylidene A_1, was quantitatively formed; aldehyde **1a** and benzoin derivative **2a** were also observed in 30% and 25% yield, respectively. The latter was formed by the reaction of the released aldehyde **1a** with **B**/**C**. These results imply that the reaction of 1,2,3-triazolylidene A_1 with aldehyde gives the Breslow intermediate reversibly. Using weakly acidic methanol as quenching agent also resulted in the formation of A_1H. Inhibition of the condensation pathway in methanol was again observed (cf. Figure 2). Importantly, the amount of benzoin **2a** formed decreased

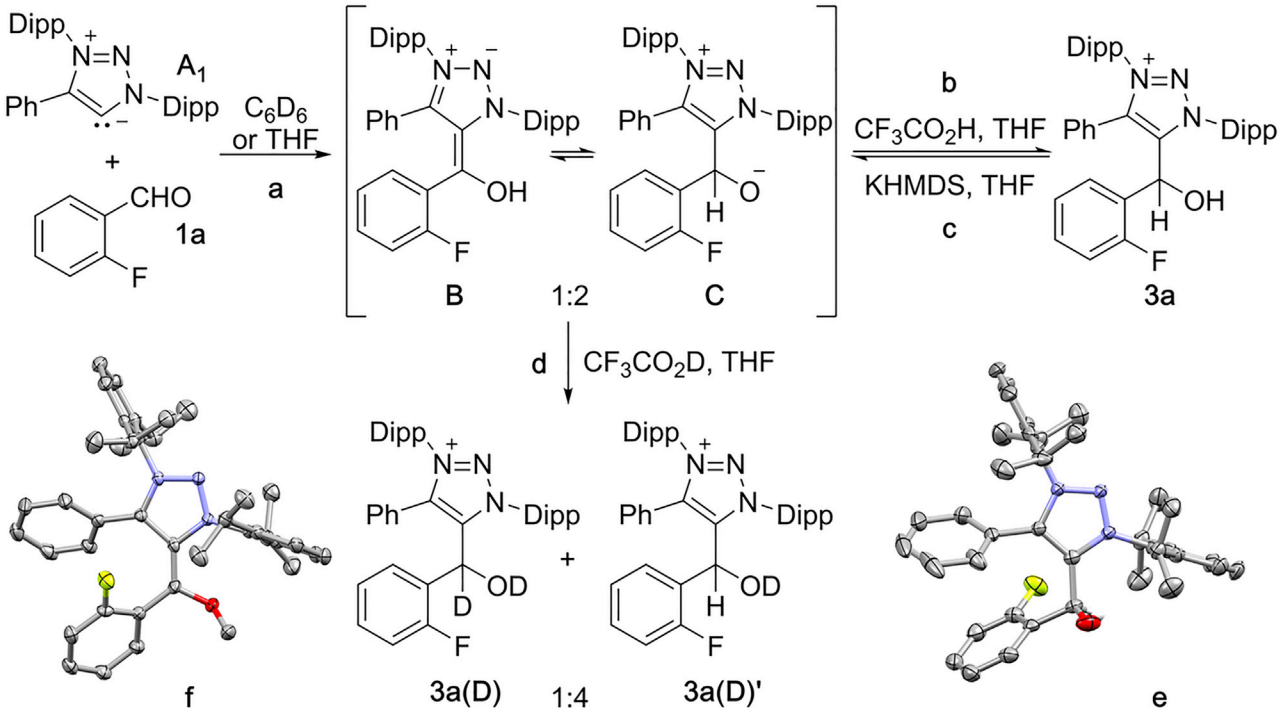
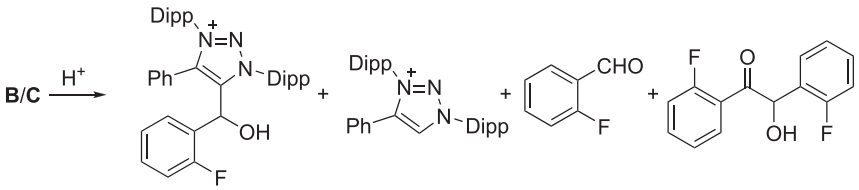


Figure 3. Evidence for the Formation of the Breslow Intermediate B and C

Stoichiometric reaction of 1,2,3-triazolylidene A_1 with aldehyde **1a** (a), protonation of Breslow intermediate **B** and **C** (b), deprotonation of triazolium **3a** by KHMDS (c), deuteration of Breslow intermediate **B** and **C** (d), and solid-state structures of **3a** (e) and **B'** (f) with 50% probability ellipsoids obtained by X-ray crystallography. Hydrogen atoms and counter-ions were removed for clarity.

significantly with increasing amounts of methanol added to the **B**/**C** solution (Figure 4). From these observations, it seems reasonable to hypothesize that methanol is sufficiently acidic to reversibly protonate **B**/**C**, limiting its concentration and thus preventing the benzoin condensation. Instead, dissociation into the aldehyde and the carbene was the prevailing outcome in this solvent.

The results summarized in Figures 3 and 4 revealed that the combination of 1,2,3-triazolylidene catalysts and methanol as the solvent was ideally suited to reversibly access the Breslow intermediate while shunting the benzoin condensation pathway and thus should favor H/D exchange reactions. To check this hypothesis, a CD_3OD solution of 4-methoxybenzaldehyde **1b** was treated with different triazolium salts **AH** (5 mol %) in the presence of tBuOK as a base (Figure 5). The 4-unsubstituted triazolium salt A_2H allowed for the recovery of aldehyde **1b** in 34% yield with 83% D-incorporation (entry 1). Under the same experimental conditions, lower D-incorporation was observed with triazolium salts A_3H, A_1H, and A_4H, but superior results were obtained with the more Brønsted acidic C-bromo (A_5H)[51,52] and C-phosphino (A_6H)[53] catalyst precursors. Indeed, using these salts, aldehyde **1b** was recovered in 54% and 70% yield with 88% and 91% D-incorporation, respectively (entries 2–6). tBuOK was found to be the most efficient base among those tested with pre-catalyst A_6H (entries 6–9). The yield and D-incorporation were increased to 87% and 97%, respectively, by raising the reaction temperature to 90°C (sealed vessels; entry 10). For comparison, imidazolium A_7H, thiazolium A_8H, 1,2,4-triazolium A_9H, and triphenylphosphine only gave low levels of D-incorporation (entries 11–14). Using the less expensive CH_3OD as deuterium source did not lead to a significant decrease in deuteration levels (entry 15). Under the same experimental conditions, but using *p*-



	3a	A_1H	1a	2a
10 eq TFA	86%	11%	9%	-
10 eq NH_4PF_6	-	99%	30%	25%
0.5 mL MeOH	55%	41%	26%	4%
1 mL MeOH	46%	52%	35%	1%
2 mL MeOH	31%	66%	63%	-
3 mL MeOH	22%	76%	73%	-

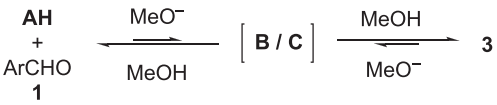
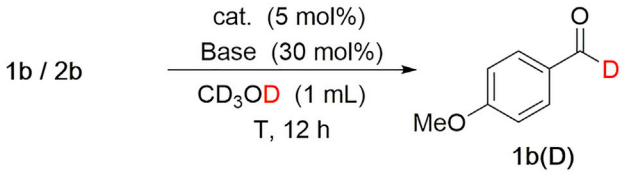


Figure 4. Protonation of Breslow Intermediate B and C and Postulated Mechanism for the Methanol Interruption of the Benzoin Condensation

B/C (0.1 mmol) in 3 mL THF with proton donor as indicated, RT, 1 h. The yields of 3a, A_1H, 1a, and 2a were determined by ^1H NMR spectroscopy with CH_2Br_2 as internal standard.

anisoin **2b** as the starting material, in place of the aldehyde **1b**, similar high yield and D-incorporation of **1b(D)** were observed (entry 16). This result indicates that in methanol, MIC catalysis of the benzoin condensation and its reversal is only kinetically competent at temperatures that thermodynamically favor the latter.[54]

With the optimized reaction conditions in hand, a variety of aldehydes **1** were investigated (Figure 6). For benzaldehydes substituted with electron-donating groups **1b–1g**, high yields and deuterium incorporation levels were achieved. Notably, a number of functional groups susceptible to interfere with transition metal-catalyzed H/D exchange reactions, including aryl iodides (**1h** and **1i**), basic amines (**1d**), and thioethers (**1e**) were tolerated. The increased steric demand of ortho-substituted benzaldehydes **1l–1n** slightly depressed the deuterium incorporation levels, but polycyclic aromatic aldehydes **1o–1q**, including the crowded 9-anthracenecarboxaldehyde **1q**, smoothly underwent H/D exchange. The O-allylated salicylaldehyde **1n** highlights the differences between the catalytic behavior of MICs **A** and other NHCs: whereas O-allylated salicylaldehydes were shown to undergo benzoin condensation under benzimidazolylidene catalysis and to cyclize into chromanones via hydroacylation of its double bond under the action of either thiazolylidene or 1,2,4-triazolylidene catalysts,[55] only the product of H/D exchange **1n(D)** was observed with MIC A_6. The reaction is compatible with redox-sensitive functional groups that would not be tolerated in classical syntheses of deuterated aldehydes. These include esters (**1k**) that would clash with synthetic routes based on the addition of nucleophilic deuteride on carboxylic acid derivatives and the ferrocenecarboxaldehyde **1r** that would not be readily accessible from the oxidation of the corresponding alcohol (RCD_2OH) because of its easily oxidized iron(II) center. Heterocyclic aldehydes **1s-1v** gave deuterated products with 88%–95% D-incorporation. The substrate scope of this reaction can be extended to alkenyl and alkyl aldehydes. α,β-Unsaturated aldehydes bearing a substituent at the α-position (**1w–1x**) were compatible, and high yields and D-incorporation were observed. Branched alkyl aldehydes **1y–1z** with a single α-substituent were somewhat less reactive, requiring extended reaction times (72–



Entry	Substrate	Cat.	Base	T (°C)	D (%)[a]	Yield (%)[a]
1	1b	A_2H	*t*-BuOK	70	83	34
2	1b	A_3H	*t*-BuOK	70	6	99
3	1b	A_1H	*t*-BuOK	70	18	99
4	1b	A_4H	*t*-BuOK	70	8	99
5	1b	A_5H	*t*-BuOK	70	88	54
6	1b	A_6H	*t*-BuOK	70	91	70
7	1b	A_6H	*t*-BuONa	70	79	52
8	1b	A_6H	DBU	70	39	54
9	1b	A_6H	DABCO	70	0	99
10	1b	A_6H	*t*-BuOK	90	97	87(82)
11	1b	A_7H	*t*-BuOK	90	9	99
12	1b	A_8H	*t*-BuOK	90	19	94
13	1b	A_9H	*t*-BuOK	90	7	95
14	1b	PPh_3	*t*-BuOK	90	0	99
15[b]	1b	A_6H	*t*-BuOK	90	91	85
16	2b	A_6H	*t*-BuOK	90	95	88

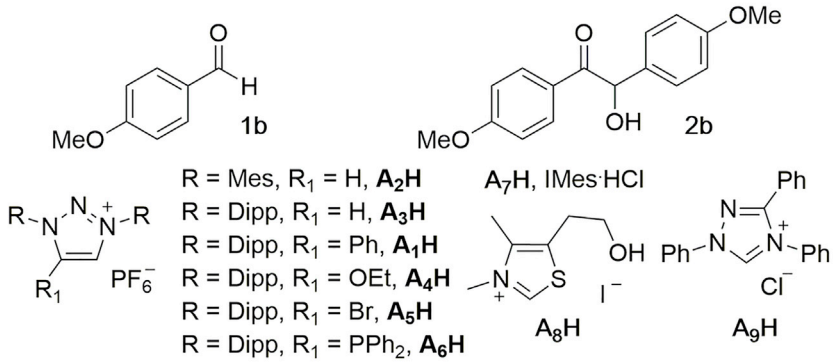


Figure 5. Optimization of 1,2,3-Triazolylidene-Catalyzed Deuteration of Aldehydes

Mes, 2,4,6-trimethylphenyl; Dipp, 2,6-diisopropylphenyl; DABCO, 1,4-diazabicyclo[2.2.2]octane; IMes, 1,3-bis(2,4,6-trimethylphenyl)imidazolinylidene. Reaction conditions: aldehyde (0.2 mmol), **AH** (5 mol %), base (30 mol %), and anhydrous CD_3OD (1 mL) for 12 h. The reactions were carried out in a 25 mL sealed tube.

[a]Deuterium incorporation [**1b(D)**/(**1b** + **1b(D)**)] and yields [(**1b** + **1b(D)**)/$\mathbf{1b}_{init}$] were determined by ^{1}H NMR spectroscopy. Isolated yield is given in parentheses.

[b]CH_3OD was employed instead of CD_3OD.

120 h) to reach high deuteration levels. Nevertheless, the steroid-derived exocyclic aldehydes **1aa**–**1ab** and the proline-derived **1ac** were also found to be suitable substrates. H/D exchange for the α,α-disubstituted aldehyde **1ad** proved to be sluggish. It is noteworthy that aldimines **1ae**–**1af** can also undergo the deuteration reaction, with 87% and 62% D-incorporation, respectively. Current limitations to the substrate

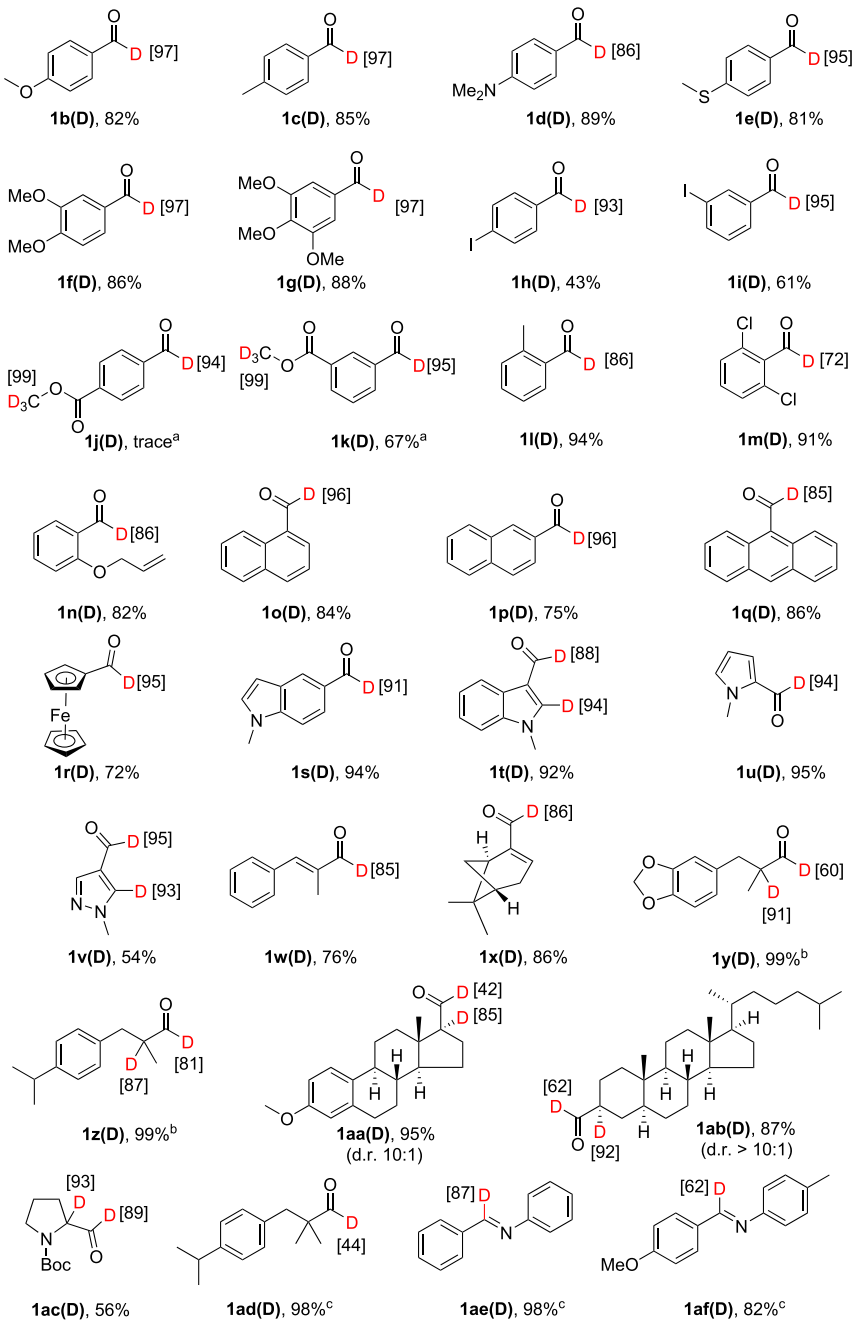


Figure 6. Substrate Scope of the 1,2,3-Triazolylidene-Catalyzed Deuteration of Aldehydes

Reaction conditions: aldehydes or imines (0.2 mmol), A_6H (0.01 mmol), and ^{t}BuOK (0.06 mmol) in CD_3OD (1 mL) at 90°C for 12 h. Isolated yields are given, and deuterium incorporation determined by ^{1}H NMR spectroscopic analysis is indicated within square brackets.

[a]Transesterification reaction occurred with CD_3OD.

[b]120 h.

[c]72 h.

scope include α-unsubstituted cinnamaldehydes, which readily undergo internal redox esterification;[43,44,56] the more readily enolizable linear alkyl aldehydes, which are susceptible to aldol-type side reactions under basic conditions; finally, highly electron deficient benzaldehydes (e.g., **1j**) also fared poorly.

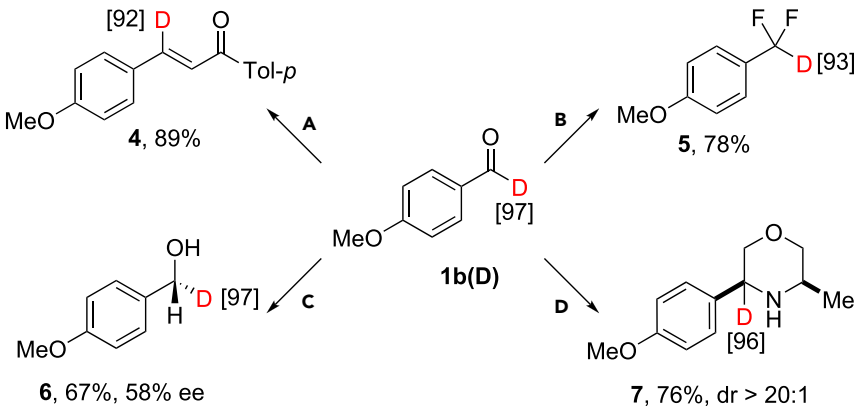


Figure 7. Synthesis of Deuterated Compounds from the Deuterated Aldehyde 1b(D)

(A) Aldol condensation of **1b(D)** with 4-methylacetophenone.

(B) Reaction of **1b(D)** with DAST.

(C) Midland reduction of **1b(D)** with Alpine borane.

(D) Reaction of **1b(D)** with Bode's SnAP reagent.

The one-step preparation of deuterium-labeled aldehydes from their protio precursors greatly simplifies the synthesis of deuterated compounds of interest as mechanistic and metabolic probes (Figure 7). Aldol condensation of **1b(D)** with 4-methylacetophenone afforded the β-deuterated chalcone derivative **4** in 89% yield and 92% D-incorporation. Reaction of **1b(D)** with *N*,*N*-diethylaminosulfur trifluoride (DAST) afforded **5** (78% yield, 93% D-incorporation), demonstrating a facile access to a deuterated difluoromethyl group, a popular lipophilic bioisostere of alcohols, thiols, or hydroxyamic acids in medicinal chemistry.[57] Midland reduction of **1b(D)** with Alpine borane gave the chiral enantiomerically enriched benzyl alcohol **6**, a known precursor to diverse chiral methylene and methyl groups,[58] in 67% yield and 97% D-incorporation with 58% ee. Finally, reaction of **1b(D)** with Bode's SnAP reagent[59,60] provided a rapid and efficient route to the stereospecifically D-labeled heterocycle **7** in 76% yield with negligible loss of D-incorporation.

We have shown that 1,2,3-triazolylidenes, a class of carbene widely used as ligands for transition metals,[61] but so far shunned in organocatalysis, react with aldehydes to form mesoionic analogs of the Breslow intermediate. The formation of the latter is rapid but reversible, and methanol inhibits the benzoin condensation. This allows 1,2,3-triazolylidenes to catalyze the H/D exchange of formyl groups. The use of MICs as catalysts in the direct conversion of protio aldehydes into their deutero congeners makes it unnecessary to use redox concession steps and avoids the use of costly transition metal catalysts. The wide scope, high yields, and deuterium incorporation levels, which extends to aryl, alkenyl, and alkyl aldehydes, coupled with the versatility of aldehydes as synthetic intermediates, make the exchange reaction an appealing option for the expedited synthesis of valuable deuterium-labeled synthons. The marked differences found between the properties of the Breslow intermediates formed from 1,2,3-triazolylidenes and those derived from the more widely used imidazol(in)ylidenes, thiazolylidenes, and 1,2,4-triazolylidenes let us envision that new types of organocatalytic reactions may yet to be discovered with MICs and for other overlooked families of persistent carbenes.

EXPERIMENTAL PROCEDURES

Full experimental procedures are provided in the Supplemental Information.

DATA AND CODE AVAILABILITY

Crystallographic data for the structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under accession numbers CCDC: 1904320 (**3a**) and CCDC: 1946731 (**B′**). Copies of the data can be obtained free of charge from www.ccdc.cam.ac.uk/structures/. All other data supporting the findings of this study are available within the article and its Supplemental Information or from the corresponding author upon reasonable request.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr.2019.08.011.

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AUTHOR CONTRIBUTIONS

X.Y., G.B., and J.B. conceived and designed the project and wrote the manuscript. W.L., L.-L.Z., M.M., L.C., and X.X. conducted the experiments and analyzed the data. M.M. and J.B. carried out the computational analyses. All authors provided comments on the experiments and the manuscript during its preparation.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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