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Catalytic Deuteration of Aldehydes with D_2O

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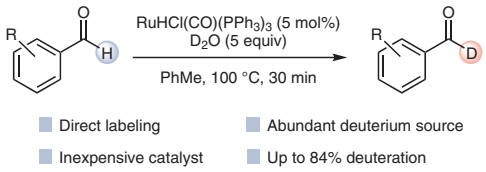
Dedicated to Professor Victor Snieckus on the occasion of his 80th birthday



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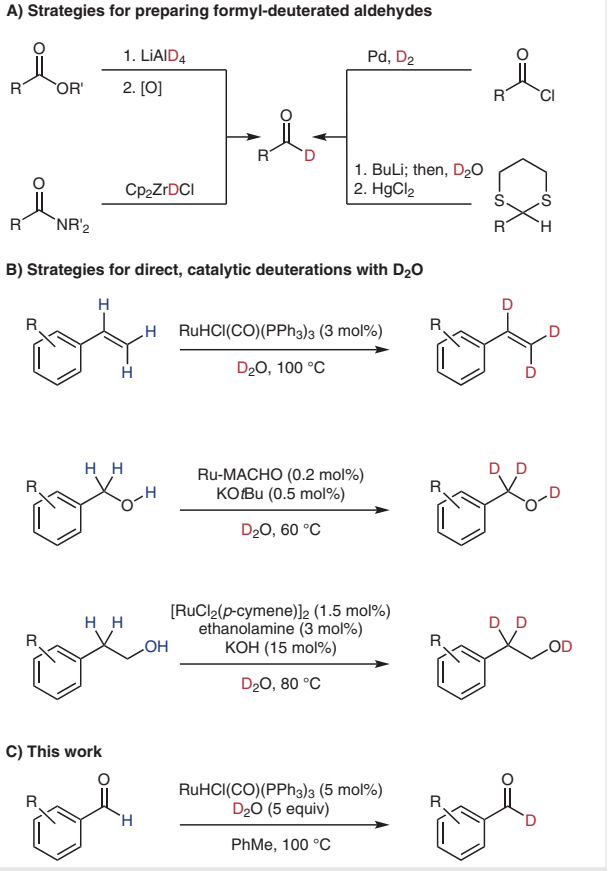
Abstract A procedure is presented that enables the direct deuteration of the formyl C–H bond of aldehydes using D_2O as the deuterium source and commercially available $RuHCl(CO)(PPh_3)_3$ as the catalyst. Up to 84% deuterium incorporation can be achieved in a single experiment. Multiple iterations can be carried out to further increase the deuteration.

Key words aldehydes, isotopic labeling, ruthenium, deuteration, H/D exchange

Deuterated molecules have a range of practical applications including use as pharmaceuticals and tools for probing reaction mechanisms and metabolic pathways.[1] Many strategies have been developed for accessing deuterated molecules; however, most require multiple chemical steps and/or use expensive deuterated reagents. For the preparation of formyl-deuterated aldehydes, reduction of the corresponding ester with lithium aluminum deuteride and subsequent oxidation is most common (Scheme 1, A).[2] Other methods include treatment of amides with Cp_2ZrDCl,[3] Rosenmund reduction of acid chlorides with D_2 gas,[4] and H/D exchange of dithianes.[5] The ideal method for preparing deuterated aldehydes would be to treat the parent aldehyde directly with an inexpensive deuterating agent.[6] Unfortunately, such strategies are rare.[7,8]

Over the past decade, a growing number of methods has been developed for directly deuterating molecules using readily available catalysts and D_2O as an abundant, inexpensive deuterium source (Scheme 1, B). For example, direct H/D exchange of olefins has been achieved by direct treatment with a ruthenium catalyst and D_2O as both solvent and deuterium source.[9] Alcohols have been selectively deuterated at the α- or α,β-positions using the commercially available ruthenium hydride catalyst Ru-MACHO.[10] The alcohol β-position can also be deuterated while maintaining protium in the α-position using a ruthenium(II)–etha-

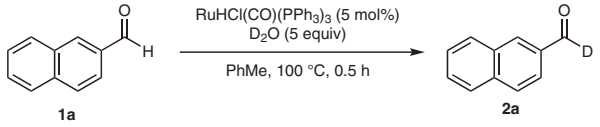


Scheme 1 Strategies for synthesizing deuterium-labeled molecules

nolamine catalyst system.[11] Reactions within this family are generally proposed to occur by a series of H/D exchange, ligand substitution, insertion, and deinsertion reactions of the metal catalyst. Given the challenges associated with the synthesis of formyl-deuterated aldehydes, we sought to explore a similar strategy using aldehydes rather than olefins or alcohols as substrates. Herein, we present how good yields and modest to good formyl-selective deuterium incorporation can be achieved directly from the parent aldehyde (Scheme 1, C).

The transformation of 2-naphthaldehyde (**1a**) into its formyl-deuterated analogue **2a** was chosen for reaction development. $RuHCl(CO)(PPh_3)_3$ was selected as the catalyst due to its ease of synthesis from inexpensive $RuCl_3$.[12] Preliminary studies with structurally related $RuH_2(CO)(PPh_3)_3$, $RuHCl(PPh_3)_3$, and $RuHCl(CO)(PCy_3)_3$ showed them to be less effective than $RuHCl(CO)(PPh_3)$. The optimal conditions identified used 5 mol% catalyst and five equivalents of D_2O in toluene (0.2 M), stirring for 30 minutes at 100 °C (Table 1). With these conditions, 72% deuterium incorporation of 2-naphthaldehyde was obtained (Table 1, entry 1). Counterintuitively, the use of more equivalents of D_2O led to a decrease in deuterium incorporation (Table 1, entries 2–4).

Table 1 Optimization of the Catalytic Formyl-Deuteration Reaction



1a 2a

Entry	Deviation from optimal reaction conditions	Deuteration (%)[a]
1	none	72
2	10 equiv D_2O	41
3	20 equiv D_2O	52
4	D_2O as solvent	18
5	$RuH_2(CO)(PPh_3)_3$ as catalyst	21
6	$Ru_3(CO)_{12}$as catalyst	trace
7	Ru-MACHO	trace
8	dppf (5 mol%) as an additive	trace
9	BINAP (5 mol%) as an additive	68
10	3 mol% catalyst loading	64
11	10 mol% catalyst loading	85
12	0.05 equiv $PhCO_2H$ as an additive	trace
13	1 equiv K_2CO_3 as an additive	30
14	1 equiv Et_3N as an additive	47
15	no exclusion of air and moisture	68

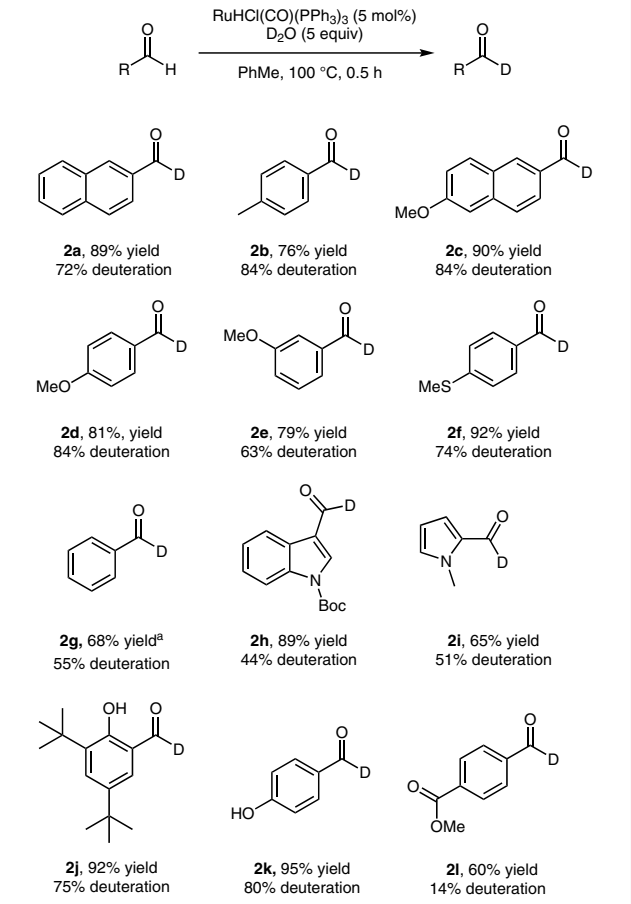
[a] Deuterium incorporation determined by integration of the residual formyl proton in ^1H NMR.

The use of alternative ruthenium catalysts (Table 1, entries 5–7) or the addition of ligands (Table 1, entries 8, 9) was not beneficial; however, catalyst loadings can have a significant influence on the reaction (Table 1, entries 10, 11). Carboxylic acids are common impurities in aldehydes. In order to test its effects, a reaction was spiked with 0.05 equivalents of benzoic acid, which completely inhibited the reaction (Table 1, entry 12). Unfortunately, basic additives such as K_2CO_3 (Table 1, entry 13) and Et_3N (Table 1, entry 14) also inhibited the reaction, so the use of pure starting material is critical for obtaining high levels of deuteration. Finally, the reaction was performed in an open vessel with no attempts made to exclude moisture and oxygen, in which only minor loss in deuterium incorporation was observed (Table 1, entry 15). In contrast to other known methods,[13] no notable deuterium incorporation into the aromatic ring was observed in any of the above reactions. The ability to selectively deuterate the formyl position of the aldehyde is advantageous and offers a distinct advantage compared to similar transformations reported in the primary literature.[8]

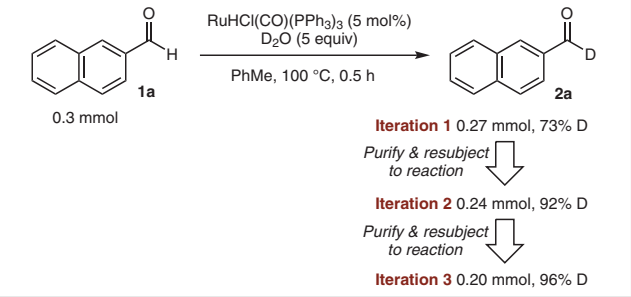
The robustness and generality of the transformation was then evaluated (Scheme 2).[14] Deuterated naphthaldehyde **2a** was isolated in 89% yield after purification by column chromatography, indicating that minimal decomposition and side-product formation occurs. A range of substituted electron-neutral and electron-rich aryl aldehyde derivatives gave between 50% and 84% deuterium incorporation (**2b–g**). Heterocyclic indole (**2h**) and pyrrole (**2i**) aldehydes were also prepared, albeit with modest deuterium incorporation. The reaction was tolerant of unprotected phenolic groups in the *ortho* (**2j**) or *para* (**2k**) positions. In contrast, electron-poor substrates such as methyl 4-formylbenzoate (**2l**) provided poor deuterium incorporation. Aliphatic aldehydes proved similarly challenging, primarily due to the formation of side-products that prohibited straightforward isolation and analysis.

Many applications of deuterated molecules require highly pure compounds with very high deuterium incorporation. To determine the viability of the process for these instances, an iterative process was explored. Starting from 0.3 mmol of naphthaldehyde (**1a**), three sequential reactions and rapid purifications were carried out (Scheme 3). The first iteration provided 0.27 mmol of **2a** (90% yield) with 73% deuterium incorporation. Resubjection of the material to the reaction conditions and further purification for a second and third iteration ultimately provided 0.20 mmol of **2a** with 96% deuterium incorporation.

While thorough evaluation is required to get a detailed understanding of reaction mechanism, a reasonable proposal can be made from precedent literature. It has been shown in stoichiometric experiments that ruthenium hydrides can exchange with D_2O to form ruthenium deuterides and HDO.[9] Furthermore, the insertion and elimina-

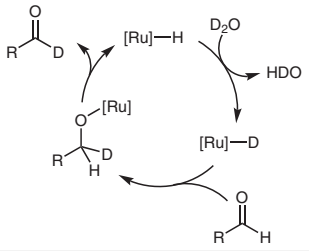


Scheme 2 Scope of aldehyde H/D exchange in D_2O. *Reagents and conditions*: Aldehyde (0.3 mmol), $RuHCl(CO)(PPh_3)_3$ (0.015 mmol), D_2O (1.5 mmol), and toluene (1.5 mL) were heated in a sealed vial for 30 min. Deuterium incorporation was determined by integration of the ^1H NMR spectra of both the crude and purified products. 'Yield' refers to the amount of both the H- and D-containing product obtained after purification. [a] Yield determined by crude ^1H NMR analysis due to volatility of the product.



Scheme 3 Iterative deuteration experiments enable access to increasingly deuterium-enriched material

tion of carbonyls into ruthenium hydride bonds is a well-established step in transfer hydrogenation and related reactions.[15] A plausible mechanism would, thus, be a combination of these steps (Scheme 4). Exchange of the hydride with a deuterium from D_2O can occur to provide a ruthenium deuteride intermediate. Coordination and insertion of the aldehyde would give a ruthenium alkoxide bearing one deuterium and one protium on the alkoxide α-carbon. Subsequent β-hydride elimination would provide the formyl-deuterated aldehyde product and regenerate the initial ruthenium hydride. Given the near thermoneutral nature of the transformation, each step is likely in equilibrium. As a consequence, a reasonable maximum deuterium incorporation of 91% can be expected when using five equivalents of D_2O. The more modest deuterium incorporation in the reaction, as well as the decrease in deuteration when using larger quantities of D_2O (Table 1, entries 1–3), suggest that the activity and potential deactivation of the catalyst also plays a significant role in the reaction outcome, and further catalyst development may lead to further improvements.



Scheme 4 A plausible reaction mechanism

In conclusion, a new method for the direct deuteration of the formyl C–H bond of aldehydes has been developed. The reaction uses an inexpensive, abundant ruthenium catalyst to facilitate the reaction with five equivalents of D_2O as the deuterium source. Moderate to good deuterium incorporation can be achieved in the 30 minute reaction time, provided that pure aldehydes with minimal carboxylic acid impurities are used. Excellent deuterium incorporation can be achieved if the product is resubjected to the reaction conditions. While more limited in scope than classical stoichiometric methods for generating deuterated aldehydes, and acknowledging the effectiveness of the recently published iridium-catalyzed systems,[8] the current approach is remarkably simple, inexpensive, and direct, making it a potentially appealing additional method for application in this general area.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588540.

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(14) **Representative Procedure for Aldehyde Deuteration**
2-Naphthaldehyde (**1a**, 46.9 mg, 0.3 mmol) and $RuHCl(CO)(PPh_3)_3$ (14.3 mg, 0.015 mmol, 5 mol%) were dissolved in PhMe (1.5 mL, 0.2 M) in an oven-dried screw-cap vial. D_2O (27 µL, 1.5 mmol) was then added. The vial was sparged with argon and capped. The resulting solution was heated to 100 °C and stirred for 30 min. At the end of the reaction, the solvent was removed in vacuo and the crude material was purified by column chromatography using a 2 → 8% EtOAc in hexane gradient to afford 41.9 mg **2a** as a white solid (89% yield, 72% D). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 1 H), 8.02–7.90 (m, 4 H), 7.67–7.57 (m, 2 H). Residual formyl proton: δ = 10.1.

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