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A simple, efficient, and selective deuteration via a flow chemistry approach

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ABSTRACT

A simple and efficient deuteration methodology has been established for a wide variety of substrates using a continuous flow hydrogenation reactor. The described procedure is many times faster (1 mg min^{-1}) compared to literature methods and the purity of the crude product can be as high as 99%. The deuterium source is D_2O, the consumption of which is very low.

Deuterium-labeled compounds are widely used as research tools in life, environmental and materials sciences.[1] They are important, for example, as, (i) internal standards in mass spectrometry,[2] (ii) tools for the elucidation of mechanisms,[3] (iii) materials with which to investigate pharmacokinetics,[4] and (iv) compounds facilitating signal assignment and structure determination in NMR spectroscopy.[5,6] Conventional techniques for the synthesis of deuterated compounds utilize D_2 gas as a deuterium source.[7] D_2 is produced commercially by one of the following procedures: (i) large-scale electrolysis of D_2O, (ii) fractional distillation of liquid hydrogen, (iii) pyrolysis of UD_3,[8] or (iv) reactions of D_2O with sodium, iron, or magnesium.[9] These methods suffer from various drawbacks on the laboratory scale such as difficulties in gas handling, cryogenic conditions, production of radioactive waste or a large quantity of metal sludge. Catalytic exchange methods have also been described, but the deuterium incorporation efficiencies varied appreciably.[10] Numerous catalytic H–D exchange reactions between H_2 and D_2O have been reported in the literature. However, these time-consuming methods do not produce high-purity D_2 and they also require high pressure, the use of a special catalyst or an excess amount of a strong base or acid.[11–14] Flow chemistry approaches are commonly used in organic synthesis.[15,16] Among flow chemistry techniques, the best-characterized and most widely used reaction is heterogenous hydrogenation.[17,18] The present work focuses on a time- and cost-efficient synthesis of deuterated compounds using Pd- or Ni-catalyzed deuteration in a continuous flow (CF) reactor combined with on-demand pressure-controlled electrolytic D_2 production. The experimental set-up allows fine-tuning of pressure, temperature, and flow rate (Fig. 1).

The deuterated products were characterized by HPLC, mass spectrometry, and NMR spectroscopy (^1H and ^2H). The deuterium contents were determined from the relative intensities of the ^1H NMR indicator resonances. First, the optimum conditions were determined for the CF deuteration of unsaturated carbon–carbon bonds with respect to the catalyst and solvent. For the Pd-catalyzed test reactions, cinnamic acid was chosen (Scheme 1).

The study started with 10% Pd/C as catalyst, according to the literature,[12] and methanol as solvent. The deuterium incorporation was only 30%, and the solvent was therefore changed to aprotic ethyl acetate, which significantly increased the incorporation of deuterium.

Nevertheless, the deuteration level referenced to the aromatic signals was still below optimal. The ^2H NMR and MS spectra

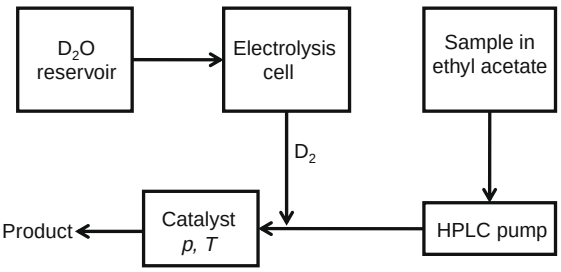

Figure 1. Schematic representation of the continuous flow deuteration reactor.

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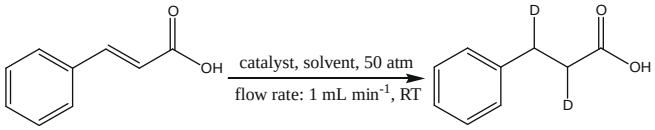


Scheme 1. Deuteration of cinnamic acid.

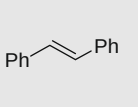
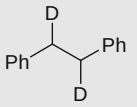
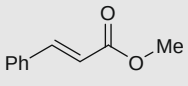
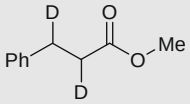
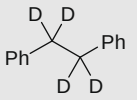
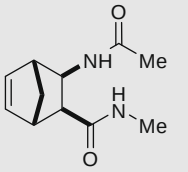
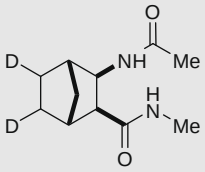
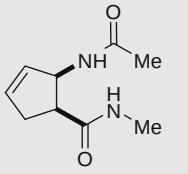
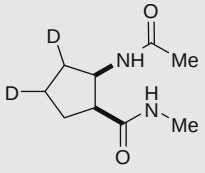
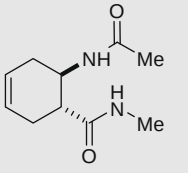
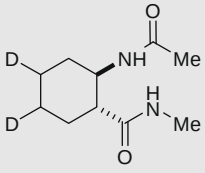
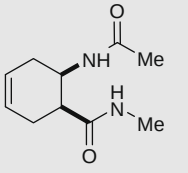
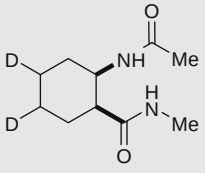
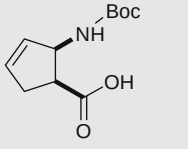
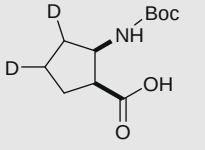
Table 1
Optimization of the reaction conditions

Entry	Catalyst	Solvent	D content (%)
1	10% Pd/C	Methanol	30
2	10% Pd/C	Ethyl acetate	70
3	5% Pd/$BaSO_4$	Ethyl acetate	95

revealed that the phenyl ring was partially saturated with deuterium also, thereby biasing the apparent degree of deuteration. The regioselectivity of the reaction could be improved using the less active catalyst (5%) Pd/$BaSO_4$ in ethyl acetate (Table 1), which consequently further elevated the apparent deuterium incorporation ratio observed on the aliphatic carbons. These values are highly competitive as compared with the literature methods mentioned above.[12,13] A pressure in the 40–60 atm range and flow rate in the range 0.7–2 mL min^{-1} did not influence the yield or the degree of deuterium incorporation. It is important to note that the reactions were carried out in a single run and the products were analyzed without any further purification. On the basis of the promising results obtained with cinnamic acid, the deuteration of various unsaturated substrates was performed in the CF system with ethyl acetate as solvent and 5% Pd/$BaSO_4$ as catalyst at room temperature (Table 2). The substrates were selected to include a range of functional groups so as to establish the performance of the CF deuteration methodology. The selection covered foldamer (unnatural folding systems) building blocks also, as the incorporation of deuterium offers new possibilities for the elucidation of the structures of these intriguing substances, where bacterial labeling is not possible.[19–21] The successful deuteration (high yield/high D%) of these compounds supports the view that the proposed experimental CF deuteration set-up is generally applicable in deuterium labeling tasks for carbon–carbon multiple bonds. The deuterium incorporation for entries 4–8 in Table 2, is cis-selective. The relative configurations have not been determined as yet.

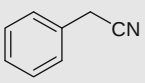
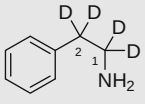
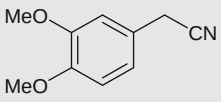
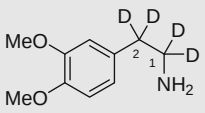
Another approach with which to introduce deuterium into molecules through simple chemistry is deuteration of a nitrile group. In accordance with the reaction conditions described in the literature, Raney nickel catalyst was applied at atmospheric pressure and a temperature of 80 °C.[17] In this case, H_2O contamination

Table 2
Deuteration of selected compounds containing a carbon–carbon multiple bond

Entry	Substrate	Product	D[a] (%)	Yield[b] (%)
1			99	99
2			97	98
3			93	97
4			96	98
5			96	99
6			95	99
7			97	95
8			98	98

[a] Deuterium content in %.
[b] Isolated yield.

Table 3
Deuteration of selected nitrile derivatives

Entry	Substrate	Product	D[a] (%)	Yield[b] (%)
1			C_1 89 C_2 33	85
2			C_1 90 C_2 17	70

[a] Deuterium content in %.
[b] Isolated yield.

(Raney nickel is stored under water in the laboratory) was minimized by soaking the catalyst in D_2O for 24 h before placing it in the CF reactor. The solvent was dry ethyl acetate. The CF deuteration was successful on the selected model compounds even with the initial conditions (Table 3) and the yields and degrees of deuteration were higher than those previously reported.[12] However, it should be noted that by-products arising from amine addition to the imine intermediates cannot be eliminated, which explains the lower yields observed in this reaction.[17] On the other hand, these by-products could be easily removed by HPLC purification. These results indicate that CF deuteration can be extended to compounds containing a CN group.

In conclusion, we have established deuteration procedures for a wide variety of substrates in a CF hydrogenation reactor. We emphasize that the synthesis is magnitudes faster (1 mg min^{-1}) than literature methods and the purity of the crude product can be as high as 99%. The only exception is nitrile reduction, where the purification is straightforward. The D_2O consumption is very low (4.41 μL min^{-1}), which represents much higher deuterium efficiency than in earlier methods. The proposed method is convenient, cost- and time-efficient, environmentally friendly, and safe.

Acknowledgments

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Supplementary data

Supplementary data (general experimental procedures, ^1H NMR, ^2H NMR, and MS spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.050.

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