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Highly Selective Continuous-Flow Synthesis of Potentially Bioactive Deuterated Chalcone Derivatives

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The selective synthesis of various dideuterochalcones as potentially bioactive deuterium-labeled products is presented, by means of the highly controlled partial deuteration of antidiabetic chalcone derivatives. The benefits of continuous-flow processing in combination with on-demand electrolytic D_2 gas generation has been exploited to avoid over-reaction to undesired side products and to achieve selective deuterium addition to the carbon–carbon double bond of the starting enones without the need for unconventional catalysts or expensive special reagents. The roles of pressure, temperature, and residence time proved crucial for the fine-tuning of the sensitive balance between the product selectivity and the reaction rate. The presented flow-chemistry-based deuteration technique lacks most of the drawbacks of the classical batch methods, and is convenient, time- and cost-efficient, and safe.

Introduction

The chalcones are a group of aromatic enones that participate in the biosynthetic pathways of flavonoids and form the central core of a variety of important biological compounds; they are often responsible for the yellow pigmentation in plants.[1] The wide range of pharmacological effects reported for chalcones include anti-inflammatory, anticancer, and antiprotozoan activities,[2] and we have recently reported that some synthetic halogen-containing chalcone derivatives can potently promote glucose consumption in adipocytes.[3] Structure–activity relationship analyses have indicated that, besides halogen substitution, the presence of a methoxy group can positively affect antidiabetic activity. Not merely chalcones, but also various dihydrochalcones offer noteworthy pharmacological potential. Recent studies revealed the cytotoxic and antiproliferative activities of synthetic dihydrochalcones (Scheme 1 a,b),[4] and there are also valuable natural products amongst the dihydrochalcone family with various biological effects (Scheme 1 c,d),[5] such as phlorizin, a well-known antidiabetic agent that can be isolated from the bark of fruit trees (Scheme 1 e).[6]

As chalcones can readily be obtained by aldol condensation between aromatic aldehydes and acetophenone or its substituted derivatives,[3,7] the most straightforward synthesis of dihydrochalcones is catalytic reduction of the double bond of the corresponding enone. However, over-reduction of the ketone to undesired alcohols and the long reaction times needed are well-known synthetic difficulties, which limit the

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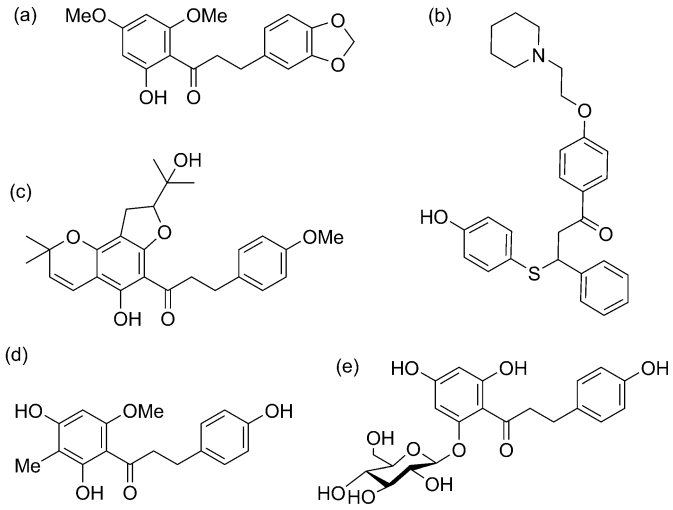


Scheme 1. Examples of dihydrochalcone derivatives with biological effects: a) cytotoxic activity,[4a] b) antiproliferative activity,[4b] c) a tyrosinase inhibitor,[5a] d) antidiabetic activity,[5b] e) phlorizin, an antidiabetic agent.[6]

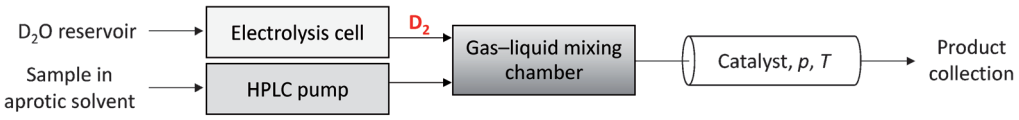


Figure 1. Schematic outline of the continuous-flow reactor.

selective and reliable production of dihydrochalcones.[8] A number of nonconventional catalysts and reagents have been reported that afford improved chemoselectivity in the reductions of α,β-unsaturated ketones, but their high costs and limited availability restrict their sustainable application.[9] On the other hand, catalytic hydrogenations can gain significant benefits through the advantageous features of continuous-flow (CF) processing,[10] especially through the unprecedented level of control over the most important reaction conditions (e.g., pressure, temperature, and flow rate), the enhanced heat and mass transfer, and the improved mixing properties.[11] Such benefits allow outstanding selectivities and reaction rates in hydrogenations, and ensure a higher operational simplicity.[12] For heterogeneous catalytic hydrogenations, the H-Cube (ThalesNano Inc.) high-pressure flow hydrogenation mesoreactor offers further improvements: it eliminates the difficulties in gas handling, greatly upgrading the operational safety, as H_2 gas is generated in situ by the electrolytic decomposition of water.[13] Thanks to its beneficial features, the H-Cube system has gained wide use in recent years, and has made a broad array of hydrogenations attainable in an inherently safer and greener manner.[14]

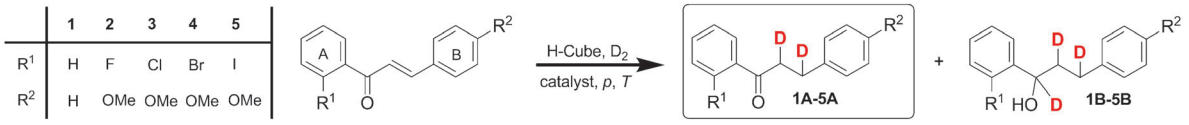
In recent years, there has been a dramatic proliferation of research involving the application of deuterium-labeled compounds.[15] Isotopic labeling studies are of considerable interest not only in chemistry, biochemistry, and the environmental sciences, but also in pharmacological research.[16] With the use of modern analytical instruments, deuterium can serve as a nonradioactive, stable isotopic tracer. For this reason, deuterium-labeled compounds can be utilized to evaluate the metabolic pathways of bioactive molecules, or in tracer studies to investigate pharmacokinetics or reaction mechanisms.[17] This prompted us to explore the partial deuteration of various chalcone derivatives and to develop a safe, simple, and rapid flow-chemistry-based technique for the highly chemoselective synthesis of a small library of dideuterochalcones, as potentially bioactive deuterium-labeled compounds.

Results and Discussion

The conventional batch synthesis of deuterated compounds suffers from several drawbacks and, in general, lacks sustainability. This is due in part to the potentially dangerous gas handling, as in the case of hydrogenations. Moreover, conventional methods for the production of D_2 gas, such as the fractional distillation of liquid hydrogen, the pyrolysis of UD_3, and reactions of D_2O with reducing agents (such as Na, Fe, or Mg), are far from perfect (cryogenic conditions, production of radioactive waste or a large quantity of metal sludge).[18] As an alternative route, catalytic H–D exchange reactions between H_2 and D_2O do not supply adequately pure D_2 gas and necessitate long reaction times.[19] We therefore established a unique and highly beneficial CF approach for deuteration reactions by changing the hydrogen source to deuterated water in an H-Cube system and generated D_2 gas continuously in small aliquots by means of the electrolytic decomposition of D_2O.[20] In this manner, the purity of the D_2 gas produced was as high as 99.9%, and the consumption of D_2O was very low, which implied much higher deuterium efficiency than in previous methods.[13] The gas generated in situ was combined with the solution of the substrate through a gas–liquid mixer, and the mixture was then transported to the catalyst bed where the triphasic reaction took place. To prevent D–H exchange and to maximize deuterium incorporation, ethyl acetate was employed as aprotic solvent. A brief outline of the CF system is shown in Figure 1.

In the first section of the study, the deuteration of *trans*-chalcone (**1**), as a simple unsubstituted model compound, was investigated with conventional heterogeneous hydrogenation catalysts to optimize the reaction conditions and to become acquainted with the basic regulatory patterns of the reaction. In the second step, various halogen-containing bioactive chalcones (**2**–**5**) were deuterated selectively to obtain substituted dideuterochalcones as potentially bioactive deuterium-labeled products. We have previously shown that the parent compounds **2**–**5** exhibit potent antidiabetic activity, which is strongly dependent on the positions of the substituents on the aromatic rings.[3] In the deuteration reactions, we aimed to exploit the benefits of continuous processing to achieve the selective formation of the dideuteroketones and to avoid undesired over-reaction to deuterated alcohols **1B**–**5B** or the reduction of the aromatic rings (Scheme 2).

Initially, 5% Pt on Al_2O_3 was chosen as heterogeneous catalyst for the deuteration of *trans*-chalcone (**1**), in view of the fact that activated charcoal as catalyst carrier can contain various protic contaminations that can easily bias the deuterium



Scheme 2. CF deuteration of *trans*-chalcone and various derivatives.

incorporation ratio.[21] Table 1 (entry 1) shows that at ambient temperature (20 °C) and atmospheric pressure, with a flow rate of 1 mL min^{-1}, a conversion of 92% was achieved, but the formation of the deuterated ketone (**1A**) was not selective, as

Table 1. Selective continuous deuteration of *trans*-chalcone (**1**) with 5% Pt/Al_2O_3 as catalyst (Scheme 2).[a]

Entry	*p* [bar]	*T* [°C]	Product ratio [%][b]		Total conv. [%][b]
			1A	**1B**	
1	1	20	78	22	92
2	10	20	59	41	98
3	20	20	55	45	98
4	30	20	46	54	98
5	40	20	27	73	99
6	40	30	24	76	99
7	40	40	21	79	98
8	50	50	15	85	99
9	50	100	11	89	100
10	100	100	0	100	100

[a] Reaction conditions: $c_1 = 1$ mg mL^{-1} in ethyl acetate, 5% Pt/Al_2O_3, 1 mL min^{-1} flow rate, no recirculation. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude material.

a substantial amount of trideuteroalcohol was formed (**1B**). (The O–D bond could not be detected, as it is converted instantly to O–H through reaction with moisture on exposure to air.) Pressurizing increases the solubility of D_2 gas, so that higher pressures expectedly lead to higher reaction rates. On gradual increase of the pressure from atmospheric to 40 bar, the conversion improved to 99%, but the formation of the deuterated ketone was suppressed by over-reduction and **1B** became the main product (Table 1, entries 2–5). Heating had similar effects on the conversion and the product selectivity: higher temperatures led to higher conversions, but promoted the over-reduction to the trideuteroalcohol (Table 1, entries 6–8). The application of high pressures allows the superheating of solvents, and we were therefore able to investigate temperatures well above the boiling point of ethyl acetate. At 50 bar and 100 °C, the conversion became quantitative with high selectivity for **1B**, and upon increase of the pressure to 100 bar at 100 °C, the formation of the deuterated alcohol was exclusive (Table 1, entries 9 and 10). It is worth mentioning that over-reaction products containing reduced aromatic rings were not detected in the reaction mixture, even under these conditions.

The above study allows the conclusion that Pt/Al_2O_3 is too active for selective dideuteroketone synthesis, even under mild conditions, and we therefore chose 5% $Pd/BaSO_4$ as a less active heterogeneous catalyst. With $Pd/BaSO_4$ at ambient temperature and pressure, at a flow rate of 1 mL min^{-1}, a conversion of only 42% and an acceptable deuterated ketone/alcohol ratio of 82:18 were obtained (Table 2, entry 1). Upon increase of the pressure to 20 and then to 40 bar, the conversion improved steeply to 70 and then to 82%, and the selectivity towards the desired dideuteroketone also increased, with product ratios of 87:13 and 89:11, respectively (Table 2, entries 2 and 3). Besides the pressure and temperature, the residence time on the catalyst bed likewise appreciably influences the rates of CF reactions.[11c,h] The residence time can be appropriately controlled by the flow rate: higher flow rates mean lower residence times and vice versa. Consequently, if the flow rate was reduced to 0.5 mL min^{-1} at room temperature and 40 bar, the rate of the reaction increased, which allowed quantitative conversion, but the undesired over-reaction to the trideuteroalcohol side product was also promoted (**1B**, Table 2, entry 4). In contrast, if the flow rate was increased to 1.5 mL min^{-1}, no over-reduction to **1B** occurred, and the desired dideuteroketone was formed exclusively, but the conversion fell to 14% (Table 2, entry 5). The overall residence time can also be improved by recirculating the eluting product mixture through the instrument. Although, on recirculation of the reaction mixture, 100% conversion could readily be achieved at a fixed flow rate of 1 mL min^{-1} (at ambient temperature and 40 bar; Table 2, entries 6 and 7), a substantial amount of over-reduction product **1B** was formed. The product ratio was found to be extremely sensitive to the reaction temperature, as heating above 30 °C resulted in over-reaction to the trideuteroalcohol and inversion of the product selectivity (Table 2, entries 8–12). Thus, the best result with $Pd/BaSO_4$ was a deuterated ketone/alcohol ratio of 89:11 with a conversion of 82% (Table 2, entry 3).

Table 2. Selective continuous deuteration of *trans*-chalcone (**1**) with 5% $Pd/BaSO_4$ as catalyst (Scheme 2).[a]

Entry	*p* [bar]	*T* [°C]	FR[b]	Runs[c]	Product ratio [%][d]		Total conv. [%][d]
					1A	**1B**	
1	1	20	1	1	82	18	42
2	20	20	1	1	87	13	70
3	40	20	1	1	89	11	82
4	40	20	0.5	1	16	84	100
5	40	20	1.5	1	100	0	14
6	40	20	1	2	27	73	100
7	40	20	1	3	9	91	100
8	1	30	1	1	71	29	46
9	40	30	1	1	81	19	90
10	1	50	1	1	15	85	88
11	50	50	1	1	13	87	94
12	50	100	1	1	9	91	96

[a] Reaction conditions: $c_1 = 1$ mg mL^{-1} in ethyl acetate, 5% $Pd/BaSO_4$. [b] FR: flow rate in mL min^{-1}. [c] Number of circulations through the CF reactor. [d] Determined by ^{1}H NMR spectroscopic analysis of the crude material.

The results in Tables 1 and 2 clearly indicate that the catalyst activity plays a key role in the determination of the product ratio; choice of a less reactive catalyst system permits a more accurate fine-tuning of the sensitive balance between the product selectivity and the conversion. Thus, to improve the selective dideuterochalcone formation, Lindlar catalyst (5% Pd on $CaCO_3$, poisoned with lead) was chosen for an additional optimization study. This performed very well at 20 °C and a flow rate of 1 mL min^{-1} with various pressures (Table 3, entries 1–4). The best results were achieved at 80 bar, at which almost complete conversion and an excellent deuterated

Table 3. Selective continuous deuteration of *trans*-chalcone (**1**) with Lindlar catalyst (Scheme 2).[a]

Entry	*p* [bar]	*T* [°C]	Runs[b]	Product ratio [%][c]		Total conv. [%][c]
				1 A	**1 B**	
1	70	20	1	86	14	95
2[d]	80	20	1	92	8	98
3	90	20	1	90	10	99
4	100	20	1	87	13	98
5	100	60	1	68	32	97
6	80	20	2	83	17	99

[a] Reaction conditions: $c_1 = 1$ mg mL^{-1} in ethyl acetate, Lindlar catalyst, 1 mL min^{-1} flow rate. [b] Number of circulations through the CF reactor. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude material. [d] Deuterium content = 98%.

ketone/alcohol ratio of 92:8 were found; higher pressures improved slightly the formation of the over-reduction product. On increasing the temperature above 20 °C, over-reduction to the subsequent alcohol occurred and the product ratio decreased (Table 3, entry 5). Recirculation through the CF reactor had a similar negative effect on the product ratio (Table 3, entry 6), and thus 80 bar, 20 °C, and 1 mL min^{-1} with a single run were accepted as the optimum conditions for the CF synthesis of **1 A** (Table 3, entry 2). The incorporation of deuterium into the chalcone skeleton was highly selective under these final conditions as, besides some minor alcohol formation, the reduction of the aromatic rings was not detectable and the deuterium content (which reflects the deuterium incorporation ratio over incidental hydrogen addition) was as high as 98%.

Substituted antidiabetic chalcones (**2**–**5**) were next subjected to deuteration for the selective synthesis of potentially bioactive dideuterochalcones. With (*E*)-1-(2-fluorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one as starting material (**2**, Scheme 2), an excellent deuterated ketone/alcohol ratio of 97:3 and a moderate conversion of 72% were obtained with Lindlar catalyst under the previously optimized reaction conditions (80 bar, 20 °C, 1 mL min^{-1} within a single run; Table 4, entry 1). The conversion was readily improved by increasing the number of discrete runs through the instrument, at the expense of a negligibly small decrease in product selectivity (Table 4, entries 2 and 3). The best results were achieved after three consecutive circulations, with a conversion of 92% and an excellent selectivity towards **2 A** (Table 4, entry 3). Similarly as for the unsubstituted model compound, with 5% Pt/Al_2O_3 under harsh reaction conditions (100 bar and 100 °C), the over-reduction determined the product ratio, selectively yielding the corresponding alcohol side product (**2 B**, Table 4, entry 4). On replacing the fluorine atom on phenyl ring A by chlorine ((*E*)-1-(2-chlorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one, **3**), CF deuteration with Lindlar catalyst (under the previously set conditions) resulted in a conversion of only 41%, and the conversion remained below the optimum after further consecutive circulations (Table 4, entries 5–7). With Pt/Al_2O_3 at 100 bar and 100 °C, complete conversion occurred, but, unlike the cases of *trans*-chalcone (**1**) and fluorine-substituted **2**, the over-reduction to the corresponding deuterated alcohol did not go to completion, and a **3 A**/**3 B** product ratio of around 1:1 was observed (Table 4, entry 8 versus Table 4, entry 4 and Table 1, entry 10). This led us to conclude that the reactivity of the chalcones in deuteration reactions depends strongly on the presence and the nature of the substituents on aromatic ring A. We next attempted the deuteration of **3** with 5% Pt/Al_2O_3 under milder conditions (100 bar and 20 °C) to limit the over-reaction. We were pleased to find that the formation of the desired dideuteroketone (**3 A**) was exclusive under these conditions, and a recirculation through the reactor led to an excellent conversion of 99% (Table 4, entries 9 and 10). CF deuteration of (*E*)-1-(2-bromophenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one (**4**) and (*E*)-1-(2-iodophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**5**) with 5% Pt/Al_2O_3 at 100 bar and 20 °C gave similar results to those for **3**. After recirculation, almost complete conversion and exclusive dideuteroketone formation were found (Table 4, entries 11, 12, 14, and 15). Interestingly, on increase of the reaction temperature to 100 °C, no over-reduction occurred, and the desired substituted dideuterochalcones could be isolated exclusively in quantitative conversions within a single run (Table 4, entries 13 and 16).

To understand the differences between the reactivities of the various chalcone derivatives, the atomic radii of the halogen substituents should be taken into consideration. In the

Table 4. Selective continuous deuteration of various halogen-containing chalcones (**2**–**5**, Scheme 2).[a]

Entry	Starting material	Catalyst	*p* [bar]	*T* [°C]	Runs[b]	Product ratio [%][c]		Total conv. [%][c]
						A	**B**	
1	**2**	Lindlar catalyst	80	20	1	97	3	72
2	**2**	Lindlar catalyst	80	20	2	96	4	82
3	**2**	Lindlar catalyst	80	20	3	95	5	92
4	**2**	5% Pt/Al_2O_3	100	100	1	5	95	97
5	**3**	Lindlar catalyst	80	20	1	97	3	41
6	**3**	Lindlar catalyst	80	20	2	99	1	47
7	**3**	Lindlar catalyst	80	20	3	100	0	60
8	**3**	5% Pt/Al_2O_3	100	100	1	52	48	100
9	**3**	5% Pt/Al_2O_3	100	20	1	100	0	90
10	**3**	5% Pt/Al_2O_3	100	20	2	100	0	99
11	**4**	5% Pt/Al_2O_3	100	20	1	100	0	92
12	**4**	5% Pt/Al_2O_3	100	20	2	100	0	98
13	**4**	5% Pt/Al_2O_3	100	100	1	100	0	100
14	**5**	5% Pt/Al_2O_3	100	20	1	100	0	93
15	**5**	5% Pt/Al_2O_3	100	20	2	100	0	98
16	**5**	5% Pt/Al_2O_3	100	100	1	100	0	100

[a] Reaction conditions: $c = 1$ mg mL^{-1} in ethyl acetate, 1 mL min^{-1} flow rate. The deuterium content was ≥97% in each experiment. [b] Number of circulations through the CF reactor. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude material.

cases of iodine and bromine, stereochemical hindrance blocks the addition of deuterium to the carbonyl group, thereby allowing excellent selectivities towards the dideuterated ketones, even under harsh reaction conditions. If a smaller substituent such as chlorine or fluorine is present, or there is no substituent in the *ortho* position from the carbonyl function, over-reduction to the corresponding alcohol is easier and the selectivity is more difficult to control. The halogen-substituted dideuterochalcones were obtained with deuterium contents of at least 97%, and reduction or partial reduction of the aromatic rings and halogen–deuterium exchange on ring A were not detected. Another beneficial feature of the CF methodology was that no workup or purification step was necessary if the conversion was quantitative and the selectivity of deuterated ketone formation was exclusive (**3A**, **4A**, and **5A**).

Conclusion

Flow chemistry in combination with on-demand electrolytic D_2 gas generation has been demonstrated to be a valuable tool for the fine-tuning of the chemoselectivity and reaction rate in deuteration reactions for the selective formation of various dideuterochalcones as potentially bioactive deuterium-labeled products. Through precise control over the most important reaction conditions (pressure, temperature, and residence time), we were able to prevent the undesired over-reaction to various side products, and to achieve the selective double-bond deuteration of aromatic enones as starting materials. The presented methodology is simple and safe as it does not involve the potentially dangerous handling of D_2 gas. Moreover, it offers a sustainable alternative to the batch-based approaches,[9a,19b,22] as it allows the attainment of high selectivity, excellent deuterium contents, and improved throughput in short process times, without the need for unconventional catalysts or expensive reagents. The biological effects of the halogen-substituted dideuterochalcones are currently undergoing evaluation in our laboratories.

Experimental Section

Materials

The reagents and materials were of the highest commercially available grade and were used without further purification. *trans*-Chalcone was purchased from Sigma–Aldrich (purity: 97%), whereas the halogen-containing derivatives were produced in our laboratories. All the synthesis procedures and characterization data can be found in a previous report.[3] Cartridges containing 5% Pt/Al_2O_3, 5% $Pd/BaSO_4$, and Lindlar catalyst were purchased from ThalesNano Inc.

General aspects of the CF deuteration

The CF deuterations were performed in an H-Cube system (ThalesNano Inc.) with change of the hydrogen source from H_2O to D_2O. The catalyst cartridge (with internal dimensions of 30×4 mm) contained approximately 100 mg of the heterogeneous hydrogenation catalyst, which was reusable after thorough washing until deactivation. The cartridge was embedded in a heating unit controlled by a Peltier system, up to a maximum of 100 °C. A backpressure regulator ensured constant pressures up to a maximum of 100 bar, and the CF of the reaction medium was provided by a conventional HPLC pump (Knauer WellChrom K-120). For the continuous reactions, solution (1 mg mL^{-1}) of the appropriate starting material (**1**–**5**) was prepared in ethyl acetate (HPLC grade). The mixture was homogenized by sonication for 3 min and was then pumped through the CF reactor under the set conditions. Between two reactions in the CF reactor, the catalyst bed was washed for 10 min with ethyl acetate at 1 mL min^{-1}. If necessary, the crude products were purified by means of column chromatography on silica gel with a mixture of *n*-hexane/EtOAc as eluent.

Product analysis

The products obtained were characterized by NMR spectroscopy and mass spectrometry (MS). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer, in $CDCl_3$ as applied solvent, with TMS as internal standard, at 400.1 and 100.6 MHz, respectively. GC–MS analyses were performed with a Thermofisher Scientific DSQ II single quadrupole GC–MS instrument, on a 30 m×0.25 mm×0.25 μm HP-5MS capillary column (Agilent J&W Scientific). The measurement parameters were as follows. Column oven temperature: from 50 to 300 °C at 10 °C min^{-1} (0–25 min), and 300 °C (25–30 min); injection temperature: 250 °C; ion source temperature: 200 °C; electrospray ionization: 70 eV; carrier gas: He, at 1 mL min^{-1}; injection volume: 5 μL; split ratio: 1:50; and mass range: 45–800 *m/z*.

The conversion and the product ratio were determined through the ^{1}H NMR spectra of the crude materials, from the relative intensities of the alkene or alkane protons of the enone starting materials and the resulting dideuteroketones and trideuteroalcohols (see the Supporting Information). The deuterium contents were determined from the relative intensities of the ^{1}H NMR indicator signals.

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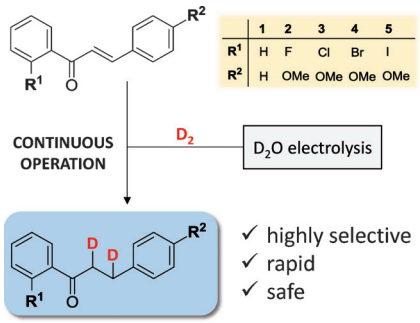
Avoiding over-reaction: Various dideuterochalcones have been synthesized selectively by means of the highly controlled partial deuteration of antidiabetic chalcone derivatives. The benefits of continuous-flow processing were exploited in combination with on-demand electrolytic generation of D_2 gas (see figure) to avoid over-reaction to undesired side products and to achieve selective deuterium incorporation without the need for special reagents.



C.-T. Hsieh, S. B. Ötvös, Y.-C. Wu, I. M. Mándity, F.-R. Chang, F. Fülöp**

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Highly Selective Continuous-Flow Synthesis of Potentially Bioactive Deuterated Chalcone Derivatives

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