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Frustrated Lewis pairs: A real alternative to deuteride / tritide reductions

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Deuterium- and tritium-labeled compounds play a principal role in tracing of biologically active molecules in complicated biochemical systems. The state-of-the-art techniques using noble metal catalysts or strong reducing agents often suffers from low functional group tolerances, poor selectivity, tricky or multistep synthesis of reagents, and low specific activity of the labeled product. Herein, we demonstrate a mild and non-metallic technique of deuteration and tritiation of polarized double bonds, such as carbonyl compounds, yielding labeled alcohols of high specific activities. This, one pot synthesis uses carrier-free hydrogen gas *in situ* activated by a freshly prepared frustrated Lewis pair, generating reducing reagents. This labeling strategy shows better selectivity and functional group tolerances compared to current reductive methods. Reported is an example of the selective reduction of the aldehyde moiety of 3-acetylbenzaldehyde. What makes this technology groundbreaking is its mildness, selectivity and generation of limited amount of radioactive waste as almost no byproducts were generated after use of $[B(C_6F_5)_3{}^3H][{}^3HTMP]$ reducing reagent. Radiochemical purity of desired ^3H-labeled product in a crude reaction mixture was determined of over 94 %. This work provides, to the community of radiochemists, a practical protocol for FLP-assisted deuterium / tritium labeling technology.

Keywords: frustrated Lewis pairs; hydrogen activation; deuterium labeled alcohol; tritium labeled alcohol; non-metallic reagent, labeled building block

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jlcr.3774

1. Introduction

The widespread use of isotopically labeled compounds have become well-established and an essential tool for the identification of drug candidates, drugs and drug metabolites in complex analytical and biochemical schemes of pharmaceutical, biological and agrochemical research.[1-9] The visualization of synthetized or isolated natural compounds is a fundamental aspect for studies of their action, affinity, and toxicity. Tritium, the most versatile radionuclide, readily labels small organic molecules of interest and is traditionally used in ligand-biological receptor-structure-activity studies or in administration, distribution, metabolism and excretion (ADME) studies.[2, 3, 10-13]

The current status of tritium chemistry methodologies comprises out of a portfolio of few fundamental synthetic approaches that radiochemist can chose from: metal-catalyzed exchange (HIE),[14-21] tritiodehalogenation,[22-28] multiple bond reduction[27, 29-31] with T_2 and tritides reduction (Figure 1).[22, 23, 32-34] The quite inert molecule of hydrogen always needs to be activated before any intended application.[35-38] The HIE approach has recently reached a significant improvement in terms of achieved specific activity (S.A.),[21, 39, 40] however, still suffers from low site-specificity label incorporation and the requirement of vast numbers of trials to develop workable reaction conditions, using up time and often the precious compound. Tritiodehalogenation represents a golden standard for hydrogen-labeling of iodinated -, brominated -, chlorinated - as well as some fluorinated synthetic precursors, providing regiospecifically labeled material possessing high S.A. The tritiation of unsaturated carbon-carbon bonds is limited by availability of the starting material and by the drawback of double bond migration throughout the carbon skeleton, due to noble metal catalyst assisted hydrogenation allowing isotopic scrambling, providing unspecific multi-labeling of desired compound. Commercially available tritides are unstable and possess low specific activity. A wide range of tritides can be freshly synthetized *in house* from carrier-free tritium with treatment of *n*BuLi-TMEDA system, producing LiT which can be used for generation of variety of boro- and aluminium-tritides, silanes or stannanes.[13, 22, 23, 32-34, 41] The synthesis of such tritides can be experimentally tricky and is always very sensitive to the quality of the reagents and the operator's skill. In house generated tritides possessing S.A. are generated in low yield and are subsequently used without isolation and purification in the complex mixture. Since these tritides are used without purification, their use in the synthesis of labeled compounds always lead to the production of many unwanted byproducts. In general, the low tolerance of harsh reagent, such as tritides and noble metal catalysts of platinum group, to other sensitive functionalities adjacent to labeled molecule is an issue every synthetic chemist need to be aware of. The need for sophisticated tritium labeling methodologies for compounds with biological importance are steadily becoming more important.

Polarized double bonds such as imines, enamines, alkylenolethers, and carbonyl compounds represent a convenient synthetic precursors for isotopic hydrogen labeling of amines, ethers and alcohols (Scheme 1). It is known that reduction of imines, enamines and silylethers can be catalyzed by FLPs,[42-44] however aldehydes reacts with FLPs stoichiometrically providing stabile alkoxyborate intermediates.[45-50] The saturation of polarized double bonds by FLPs can be described as the nucleophilic addition of hydrides to the polar double bond prior to proton transfer. The H_2-activated linked P/B system $MesPCH_2CH_2B(C_6F_5)_2$ can deliver hydride to benzaldehyde, forming the corresponding phosphonium borate zwitterion.[49] Subsequently, Repo and Rieger published analogous chemistry using bulky nitrogen bases.[46] The computational investigations by the Privalov group suggest that ketone hydrogenation using $B(C_6F_5)_3$ (**1**) as a catalyst is energetically viable.[51] Stephan,[52, 53] Ashley,[54] and the Soós[55] groups independently reported FLP-based carbonyl reduction using of weak coordinating solvent as the base. Nucleophilic ethers (Et_2O,

1,4-dioxane) were shown to be capable of reversibly splitting H_2 in combination with boron based Lewis acids, however, under conditions not applicable for tritium experiments (the need of pressurized vessel – 5-60 bar, 70-100 °C, multiple days of reaction). Recently, we have reported a study focusing on the use of the FLP-$^2H_2$ system for the reduction of carbonyl compounds under mild conditions applicable to tritium experiments (sub-atmospheric pressure).[47]

We have also confirmed the ability of the FLP system [$B(C_6F_5)_3$][2,2,6,6-tetramethylpiperidine (TMP)] to heterolytically split molecules of tritium to generate the reducing reagent [TMP^3H][$^3HB(C_6F_5)_3$].[47] Apart from reports from our group, there is no other comprehensive study in the use of FLPs for deuterium/tritium isotopic labeling of organic compounds (deuterodefluorination of alkyl C–F groups using the FLP system is communicated in our work in this special issue). Recently, Soós *et al.* reported a study in the size-exclusion design of Lewis acid for FLP-mediated deuterium reduction of both quinolone and 2-methyl-8-chloroquinolone, however, the reactions were carried out under rather harsh conditions (8 atm, 105 °C, 17h).[56]

2. Results and discussion

In our previous work we studied the reactivity of various phosphine-, carbene-, and nitrogen-based FLPs, generating appropriate FLPs, after a reaction with boron-based Lewis acid $B(C_6F_5)_3$. The most reliable reaction condition for the reduction of any carbonyl compounds proved to be the coordinative action of N-based Lewis base 2,2,6,6-tetramethylpiperidine (TMP) with $B(C_6F_5)_3$ used in 1 molar excess to the reduced substrate. Here, we further investigate the FLP-$^2H_2$ (**2**) reducing system, using commercially available material (such as ordinary carbonyl compounds) providing isotopically labeled alcohols. The desired labeled product can be used as a suitable labeled building block for further synthetic transformations.[57]

To optimize the reaction conditions for the reduction of aldehydes by the FLP-$^2H_2$ reagent (**2**), we investigated the conversion of 3-methoxybenzaldehyde (**3**) to the corresponding alcohol. The methoxy group has different chemical shift in ^1H NMR for substrate **3** and product **17**, and was effectively used to determine the conversion of substrate **3**. One equivalent of **2** afforded 74 % conversion of **3** and 56 % isolated yield of (3-methoxyphenyl)methan-[^2H]-ol (**17**) respectively. The full conversion of substrates was achievable in all cases when 1.5-2.0 eq of **2** was used. To ensure full conversion of both the activated and deactivated aldehydes, and straightforward isolation of the labeled products, we decided to use 2.0 eq of reagent **2** in further experiments. It was determined that both dry toluene and dichloromethane (Table 1) could act as suitable solvents for FLP-$^2H_2$ reduction. The reaction carried out in dry acetonitrile only afforded poor conversion of **3** (Table 1, Entry 6). The use of dry THF indicated limited applicability due to slow nucleophilic reaction of the solvent with **1**, producing a jelly-like adduct of (THF)->$B(C_6F_5)_3$, after overnight storage in the refrigerator (Table 1, Entry 7). Nitrogen-based Lewis bases proved to be unequivocally the best counterparts to $B(C_6F_5)_3$, affording high rate of substrate conversion and no byproduct formation at all. Both 2,2,6,6-tetramethylpiperidine (TMP) and 1,2,2,6,6-pentamethylpiperidine (PMP) can be conveniently used to afford similar outcomes in terms of achieved conversion, isolated yield, and isotope enrichment (S.A.).[47] On the other hand, phosphin-based Lewis base such as (tBu)$_3$P and (Mes)$_3$P provided low conversion or/and unidentified byproducts formation (Table 1, Entry 8, 9).A noteworthy and valuable aspect of this study is the fruitful use of very low pressure of hydrogen (≈ 200 mbar) for FLP-assisted hydrogen labeling, providing generally the same achievements as with the use of atmospheric pressure of hydrogen (1 bar) (Table 1). This

approach represents a high-value benefit for its use in tritium chemistry in terms of limited radioactive tritium gas consumption as well as suppression of radioactive waste generation.

The most useful aspect in the daily use of reagent **2** is the shelf-stability of a borane **1** stock solution, used for FLP *in situ* generation, when needed. Thus, long term storage was of our interest. Borane **1** dissolved in dry toluene (0.1M, 10 mL) and was stored in the refrigerator (4 °C). One portion (1 mL) was used every two weeks to carry out the reduction of aldehyde **3** under conditions displayed in Table 1, Entry 4. After two months of storage, no observable decrease of both the conversion of **3** (>99 %; determined by ^{1}H NMR and GC-MS measurements) and the ^{2}H-enrichment of product **17** (>95 %; determined by ^{1}H NMR) were witnessed. After another 6 months of storage, lower reconversion of **3** was witnessed, reaching only 91 % of product formation but still with the retention of the level of deuterium labeling.

The Lewis acid **1** is very hydrophilic, forming in the presence of water a neutral adduct of $[H_2O{\rightarrow}B(C_6F_5)_3].2H_2O$.[58] This aqua complex inhibits any further formation of the reactive frustrated Lewis pair (**2**). To study the moisture tolerance of reagent **1**, an addition of 0.5 eq of H_2O was added into a freshly prepared borane solution of **1**, before the reagent was used for FLP generation under conditions similar to Table 1, Entry 4. A diminished conversion of **3** to 92 % was witnessed. An addition of 2 eq of water completely inhibited the reaction course and no conversion was observed.

To broaden the insights into the reactivity of **2** towards various carbonyl compounds, heteroaromates (**9-14**) and isotopomers (**4-6** and **11-13**) were investigated (Table 1, Entry 12-29). The full conversion of substrates was achieved in all cases providing the appropriate labeled alcohol with ^{2}H-enrichment of over 95 %. For the isolated yields of the products, see Table 1. The same system used for aldehyde hydrogenations proved to be capable of hydrogenating 9-anthracenecarboxylate **15** to the corresponding 9,10-dihydroanthracen-9-yl-10-[^{2}H])methan-[^{2}H]-ol **29**. This reactivity is in accordance with the data of FLP hydrogenations of polycyclic aromatic hydrocarbons (PAHs) reported in literature.[59]

To investigate the affinity of **2** towards ketone functionalities, various substrates bearing a ketone moiety (**31-38**) were used in the reduction with **2** under general conditions (Table 2). The ketone moiety proved to be entirely unreactive under the general conditions, unless the ketone moiety was strongly activated by an electron withdrawing group (Table 2, Entry 1 and 2). The reduction of substrate **31**, substituted with a nitro group, provided a deuterium labeled secondary alcohol **39** in high yield with high ^{2}H-enrichment (>95 %), and showing full conversion of starting ketone **31** in a short reaction time of only 10 min.

The selectivity of $[B(C_6F_5)_3{}^{2}H][^{2}HTMP]$ (**2)** was unequivocally proven with reaction of 3-acetylbenzaldehyde (**16**), bearing both aldehyde and ketone group. Under general conditions (Table 1, Entry 31) the aldehyde functionalization was completely reduced, providing high ^{2}H-enrychment (>95 %) of the corresponding labeled alcohol **30**, leaving ketone moiety unaffected.

The successful isolation of the series of [^{2}H]-labeled alcohols was encouraging for the application of this procedure analogically for the tritium experiment. Recently, we have illustrated the ability of FLP to activate tritium molecules under subatmospherical pressure of carrier-free tritium gas (**505 mbar**), producing $[B(C_6F_5)_3{}^{3}H][^{3}HTMP]$ used in an one pot synthesis for reduction of p-(*N*-Boc)-benzaldehyde, affording the corresponding ^{3}H-labeled alcohol in high S.A. of 24.3 Ci/mmol. To optimize the conditions for routine use in

radiochemistry, we investigated the further suppression of tritium consumption, and attempted the experiment under very low pressure of carrier-free tritium gas (**190 mbar, 2.5 Ci, 93 GBq**). The successful reduction of aldehyde **3** was the definitive proof of the generation of the $[B(C_6F_5)_3{}^3H][^3HTMP]$ reducing reagent under the above mentioned conditions. To ensure the full conversion of the precursor **3** in a short time (3 h), excess of FLP (2 eq) was employed. The reduction of precursor **3** and the subsequent hydrolysis of the alkoxyborate intermediate (not isolated) gave the desired [^{3}H]-labeled benzyl alcohol **40** [full conversion of **3** according to HPLC (215 nm), Figure 2, the middle chromatogram].

What makes this technology groundbreaking is besides its mildness and selectivity, also generation of limited amount of radioactive waste as almost no byproducts were generated after reduction made by $[B(C_6F_5)_3{}^3H][^3HTMP]$; radiochemical purity of desired ^{3}H-labeled product in a crude reaction mixture was determined over 94 % [Figure 2, the bottom chromatogram, and SI of ref[47]]. We determined the activity of the prepared **40** at 509 mCi with a specific activity of 27.1 Ci/mmol (determined by ^{1}H NMR) and radiochemical purity after HPLC purification (>99 %). To our surprise, according to the $^3H\{^1H\}$ NMR spectrum of product **40**, two singlet peaks were observed. The expected singlet was observed at 4.65 ppm, however, one other additional minor singlet peak was also observed in an up field shifted position at 4.62 ppm (see Supplementary Information). Similarly, according to the ^3H-^1H coupled NMR spectrum, the product could be confirmed but with an additional doublet peak at 4.40 ppm and a minor singlet peak at 4.37 ppm which belongs to tritium double-labeled methylene (see Supplementary Information). The ratio between the integrated signal belonging to the mono-labeled alcohol and the signal belonging to the double-labeled alcohol was found to be 5:1, which accounts for the abundance of mono- and di-tritiated compound in sample of 10:1. It is noteworthy that we had not seen the introduction of two tritium atoms on reduced p-(*N*-Boc)-benzaldehyde when using the same reagent recently.[47] Moreover, we have not observed, in any case, the incorporation of two deuterium atoms on the methylene group of labeled benzaldehydes based on ^{1}H NMR spectroscopy. Mass spectrometry provided inconclusive data, possibly because of the very low amount of double labeled product (below 10 %), which overlaps with the combined $^{13}C+^{15}N$ isotopic peak of the utterly dominated monolabeled product. Additionally, because of the chemical nature and small mass of labeled alcohols, the electron-ionization technique (EI) had to be used for their ionization. Due to nature of EI, isotopic scrambling on the analyzed molecule could partly occur, providing misleading data in terms of isotopic enrichment. For this reason, mass EI technique is not ideal (accurate enough) for the determination of isotopic enrichment. One exception was the ionization of pyridin-3-yl-methan-[^{2}H]-ol (**26**) with the mild ESI technique, providing convincing data of no double labeling. Formation of double-labeled alcohol is most likely an issue of the particular substrate **3**, substituted with an electron withdrawing group in a meta-position. The mechanistic implications of the additional-tritium introduction have not been investigated. However, we hypothesize the mechanism might be based on the H/T exchange on methylene group of ^{3}H-labeled alcohol, when polarized as alkoxyborate intermediate.

To investigate the course of the reaction, a reaction was set up without the introduction of any Lewis base, as suggested Nyhlén and Privalov, for the reduction of carbonyl moieties in their computational study. In contradiction with this theory we have not achieved any conversion of benzaldehyde under the conditions we have used, even after 14 days of reaction under subatmospherical pressure of hydrogen (Scheme 3). The coordinative role of both Lewis acid and Lewis base was demonstrated to be essential to activate hydrogen molecule under such a low pressure of hydrogen. Repo and coworkers reported 29 % conversion of similar reaction when harsh conditions were employed ($^1H_2$, 2 atm, 110 °C, 48h, toluene-*d8*).[54, 60]

3. Conclusion

The need of rapid radiotracer synthesis in early stage of drug discovery has driven the research for better, selective, regio-selective, reproducible, robust, and predictable tritium incorporation techniques using ultra-mild reaction conditions providing high specific activity. A stoichiometric carbonyl reductions using the pre-hydrogenated intramolecular FLP system provided isotopically labeled alcohols in a high isolated yield using commercially available, and non-toxic reagents. This system shows high selectivity of the aldehyde functionality over ketone moiety, providing labeled alcohols as a final product or labeled building block.

4. Experimental section

4.1. General

The tritiation and deuterium reaction was performed on a custom-designed deuterium, and tritium, respectively, manifold system manufactured by RC Tritec AG, Switzerland. Activities were measured on a Perkin-Elmer TriCarb 2900TR liquid scintillation counter (LSC) in a Zinsser Quicksafe A cocktail. The HPLC was performed on a system consisting of a WATERS Delta 600 pump and controller, a WATERS 2487 UV detector and a RAMONA radio chromatographic detector from Raytest (Germany) with interchangeable fluid cells. For the preparative runs, the cell with a single small crystal of a solid scintillator was used; for analytical runs, the column effluent was mixed with a Zinsser Quickszint Flow 302 cocktail in the ratio of 1:3. The ^{1}H-, ^{13}C-NMR spectra were recorded at 300 and 400 MHz; 75 and 100 MHz with a Bruker Avance II 300 MHz, Avance III™ HD 400 MHz instrument, respectively, at 25 °C (the solvents are indicated in parentheses). Chemical shifts are reported in ppm relative to TMS. The mass spectra were obtained by the Bruker Daltonics Esquire 4000 system with direct input (ESI, acetonitrile-H_2O stream, a mass range of 50–1200 Da, Esquire Control Software). The HR-mass spectra were obtained in the ESI mode either on a Waters-Micromass Q-TOF Micro Mass Spectrometer or on a Thermo Fisher Scientific LTQ Orbitrap XLc. The mass spectra of the labeled compounds were measured on a Thermo Finnigan LCQ Classic spectrometer using electrospray ionization (ESI). Column chromatography was carried out with SiO_2 60 (a particle size of 0.040–0.063 mm, 230–400 mesh; Merck) and commercially available solvents. Thin-layer chromatography (TLC) was conducted on aluminum sheets coated with SiO_2 60 F_{254} obtained from Merck, with visualization by a UV lamp (254 or 360 nm). Borane $B(C_6F_5)_3$ was purchased from TCI Europe N.V.. 2,2,6,6-Tetramethylpiperidine was purchased from Fluorochem Ltd.. To enhanced long-term reactivity of borane, the stock solution of $B(C_6F_5)_3$ (0.1 M), was prepared under an inert atmosphere of nitrogen, using dry and distilled solvents (toluene or CH_2Cl_2), and allowed to be store in fridge (4 °C) to sustain its quality for months.

4.2. General procedure for sub-atmospherical FLP-assisted deuteration

A round-bottomed reaction flask (3 mL) with a side arm, equipped with a magnetic stir bar, was mounted onto this system and was dried by application of vacuum-inert sequence and filled with $^{2}H_2$ gas (200-1000 mbar). A 0.1M solution (dry toluene or CH_2Cl_2) of $B(C_6F_5)_3$ (2 mL, 0.2 mmol) was added to the reaction flask via the septum in the sidearm. To this solution,

2,2,6,6-tetramethylpiperidine (0.2 mmol) was added dropwise and the reaction mixture was vigorously stirred for 1 h at room temperature. To a slightly yellowish solution of $[TMP^2H][^2HB(C_6F_5)_3]$ a 1 M solution of appropriate carbonyl compound (0.1-0.2 mmol) was added via the sidearm. The reaction was monitored by TLC (SiO_2; Hexane/EtOAc/MeOH 7:3:0-1). The reaction was left to proceed until full conversion of starting material was achieved (Table 1). The alkoxyborate intermediate was hydrolyzed by addition of 1 mL of 1N HCl for 20 min, or alternatively (applicable for basic-nature substrates), by 1 mL of distilled water for 1 hour. The reaction mixture was neutralized by the addition of 1M Na_2CO_3. Separated organic phase was dried by Mg_2SO_4, and solvents were evaporated. The crude product was purified by column chromatography (SiO_2; Hexane/EtOAc/MeOH 7:3:0-1). For isolated yields see Table 1. Isotopic enrichment on the methylene position was determined by ^{1}H NMR over 95 % in all cases, as a decrease of corresponding signal in ^{1}H spectrum (see Supplementary Information).

*4.2.1. 3-Methoxyphenyl-[^{2}H]-methanol (**17**).* The title compound was prepared from **3** following general procedure. A colorless oil. (10.5 mg, 77 %). The product was purified by column chromatography (SiO_2, hexane/EtOAc, 7:3) R_f = 0.31. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.65 (1H, bs, O*H*), 3.82 (3H, s, CH_3), 4.66 (1H, s, C*H*D), 6.81–6.86 (1H, m, Ar), 6.91–6.97 (2H, m, Ar), 7.27–7.31 (1H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.4, 65.1 ($t_{1:1:1}$, *C*D, J_{CD} = 22.0 Hz), 112.4, 113.4, 119.2, 129.7, 142.6, 160.0. HRMS (TOF MS EI+): Calculated for $C_8H_9DO_2$ 139.0744. Found 139.0743.

4.2.2. *2-Fluorophenyl-[^{2}H]-methanol (**18**).* The title compound was prepared from **4** following general procedure. A colorless oil. (11.8 mg, 93 %). The product was purified by column chromatography (SiO_2, hexane/EtOAc, 7:3) R_f = 0.37. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.78 (1H, bs, O*H*), 4.75 (1H, s, C*H*D), 7.01–7.09 (1H, m, Ar), 7.15 (1H, *J* = 7.5, 1.2 Hz, Ar), 7.25–7.32 (1H, m, Ar), 7.42 (1H, tdd, J_{HH} = 7.5 and 0.6 Hz, $^4J_{HF}$ = 1.9 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 59.3 (td, *C*D, J_{CD} = 21.9 Hz, $^4J_{CF}$ = 4.6 Hz), 115.4 (d, $^2J_{CF}$ = 21.19 Hz), 124.4 (d, $^4J_{CF}$ = 3.63 Hz), 127.8 (d, $^2J_{CF}$ = 15.25 Hz), 129.4 (d, $^4J_{CF}$ = 4.50 Hz), 129.5 (d, $^3J_{CF}$ = 7.62 Hz), 160.8 (d, $^1J_{CF}$ = 247.38 Hz). HRMS (TOF MS EI+): Calculated for C_7H_6DFO 127.0544. Found 127.0546.

4.2.3. *3-Fluorophenyl-[^{2}H]-methanol (**19**).* The title compound was prepared from **5** following general procedure. A colorless oil. (8.5 mg, 67 %). The product was purified by column chromatography (SiO_2, hexane/EtOAc, 7:3) R_f = 0.24. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.71 (1H, bs, O*H*), 4.69 (1H, s, C*H*D), 6.98 (1H, tdd, $^3J_{HF}$ = 8.3 Hz, J_{HH} = 2.7 and 0.9 Hz, Ar), 7.06–7.15 (2H, m, Ar), 7.32 (1H, td, J_{HH} = 7.8 Hz, $^4J_{HF}$ = 5.8 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 64.4 (td, *C*D, J_{CD} = 22.1 Hz, $^5J_{CF}$ = 1.8 Hz), 113.8 (d, $^2J_{CF}$ = 21.22 Hz), 114.5 (d, $^2J_{CF}$ = 21.22 Hz), 122.3 (d, $^4J_{CF}$ = 2.92 Hz), 130.2 (d, $^3J_{CF}$ = 8.47 Hz), 143.5 (d, $^3J_{CF}$ = 7.31 Hz), 163.1 (d, $^1J_{CF}$ = 246.89 Hz). HRMS (TOF MS EI+) Calculated for C_7H_6DFO 127.0544. Found 127.0546.

*4.2.4. 4-Fluorophenyl-[^{2}H]-methanol (**20**).* The title compound was prepared from **6** following general procedure. A colorless oil. (10.0 mg, 79 %). The product was purified by column chromatography (SiO_2, hexane/EtOAc, 7:3) R_f = 0.25. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.67 (1H, bs, O*H*), 4.64 (1H, s, C*H*D), 7.01–7.09 (2H, m, Ar*H*), 7.29–7.38 (2H, m, Ar). ^{13}C NMR

(100 MHz, $CDCl_3$) δ: 64.5 (t, *C*D, J_{CD} = 21.98 Hz), 115.5 (d, $^2J_{CF}$ = 21.36 Hz), 128.9 (d, $^3J_{CF}$ = 7.80 Hz), 136.6 (d, $^4J_{CF}$ = 3.02 Hz), 162.5 (d, $^1J_{CF}$ = 240.31 Hz). HRMS (TOF MS EI+): Calculated for C_7H_6DFO 127.0544. Found 127.0547.

4.2.5. *4-Chlorophenyl-[^{2}H]-methanol (**21**).* The title compound was prepared from **7** following general procedure. A yellowish oil. (11.8 mg, 83 %). The product was purified by column chromatography (SiO_2, hexane/EtOAc, 7:3) R_f = 0.38. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.00 (1H, bs, O*H*), 4.59 (1H, s, C*H*D), 7.20–7.24 (2×1H, m, Ar), 7.31–7.35 (2×1H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 64.8 ($t_{1:1:1}$, *C*D), 128.6, 129.0, 134.2, 137.7. HRMS (TOF MS EI+): Calculated for C_7H_6DClO 143.0248. Found 143.0247.

4.2.6. *Phenyl-[^{2}H]-methanol (**22**).* The title compound was prepared from **8** following general procedure. A yellowish oil. (10.1 mg, 93 %). The product was purified by column chromatography (SiO_2, hexane/EtOAc, 7:3) R_f = 0.31. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.65 (1H, bs, O*H*), 4.68 (1H, s, C*H*D), 7.27–7.39 (5×1H, m, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 65.2 ($t_{1:1:1}$, *C*D), 127.1, 127.8, 128.7, 140.9. HRMS (TOF MS EI+): Calculated for C_7H_7DO 109.0638. Found 109.0636.

4.2.7. *2-Thiophene-[^{2}H]-methanol (**23**).* The title compound was prepared from **9** following the general procedure. A yellowish oil. (7.9 mg, 69 %). Purified by column chromatography (SiO_2, hexane/EtOAc, 7:3) R_f = 0.33. ^{1}H NMR (400 MHz, CDCl3) δ: 1.74 (1H, bs, O*H*), 4.83 (1H, s, C*H*D), 6.99 (1H, dd, *J* = 5.0 and 3.5 Hz, Ar), 7.03 (1H, ddd, *J* = 3.5 and 1.3 and 0.8 Hz, Ar), 7.29 (1H, dd, *J* = 5.0 and 1.3 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 59.9 ($t_{1:1:1}$, *C*D), 125.6, 125.8, 127.0, 144.0. HRMS (TOF MS EI+): Calculated for C_5H_5DOS 115.0202. Found 115.0200.

4.2.8. *(1-Methyl-1H-imidazol-5-yl)-[^{2}H]-methanol (**24**).* The title compound was prepared from **10** following general procedure. An amorphous solid. (7.7 mg, 69 %). The product was purified by column chromatography (SiO_2, hexane/EtOAc/MeOH, 7:3:0.5) R_f = 0.28. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.82 (1H, bs, O*H*), 3.88 (3H, s, CH_3), 4.66 (1H, s, C*H*D), 6.97 (1H, s, Ar), 7.79 (1H, s, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.8, 53.7 ($t_{1:1:1}$, *C*D, J_{CD} = 22.0 Hz), 125.1, 132.0, 138.2. HRMS (TOF MS EI+): Calculated for $C_5H_7DN_2O$ 113.0699. Found 113.0703.

4.2.9. *2-Pyridine-[^{2}H]-methanol (**25**).* The title compound was prepared from **11** following general procedure. A yellow oil. (6.7 mg, 63 %). The product was purified by column chromatography (SiO_2, hexane/EtOAc 7:3) R_f = 0.22. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.68 (1H, s, C*H*D), 4.84 (1H, bs, O*H*), 7.78 (1H, d, J_{HH} = 8.2 Hz, Ar), 7.91 (1H, t, J_{HH} = 6.8 Hz, Ar), 8.45 (1H, t, J_{HH} = 8.0 Hz, Ar), 8.68 (1H, d, J_{HH} = 6.0 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 61.0 (t, *C*D, J_{CD} = 22.71 Hz), 125.3, 139.5, 140.6, 144.8, 145.7. HRMS (TOF MS EI+): Calculated for C_6H_6DNO 110.0590. Found 110.0682.

4.2.10. *3-Pyridine-[^{2}H]-methanol (**26**).* The title compound was prepared from **12** following general procedure. A colorless oil. (9.6 mg, 87 %). The product was purified by column chromatography (SiO_2, hexane/EtOAc/MeOH 7:3:1) R_f = 0.46. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.23 (1H, bs, O*H*), 4.85 (1H, s, C*H*D), 7.67 (1H, dd, J_{HH} = 8.14 and 6.04 Hz), 8.17 (1H, d,

J_{HH} = 6.13 Hz, Ar), 8.52 (1H, m, Ar), 8.59 (1H, s, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 61.0 ($t_{1:1:1}$, *C*D, J_{CD} = 22.71 Hz), 125.3, 139.5, 140.6, 144.8, 145.7. HRMS (ESI+): Calculated for C_6H_7DNO $[M+H]^+$ 111.0669. Found 111.0663.

4.2.11. *4-Pyridine-[^{2}H]-methanol (**27**).* The title compound was prepared from **13** following general procedure. An morphous solid. (8.9 mg, 81 %). The product was purified by column chromatography (SiO_2, hexane/EtOAc 7:3) R_f = 0.27. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.17 (1H, bs, O*H*), 4.94 (1H, s, C*H*D), 7.67 (2H, d, J_{HH} = 6.54, Ar), 8.53 (2H, d, J_{HH} = 6.13, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 62.3 ($t_{1:1:1}$, *C*D, J_{CD} = 21.9 Hz), 122.4, 146.5, 158.1. HRMS (TOF MS EI+) Calculated for C_6H_6DNO 110.0590. Found 110.0592.

4.2.12. *Isoquinoline-[^{2}H]-methanol (**28**).* The title compound was prepared from **14** following general procedure. An amorphous solid. (13.1 mg, 82 %). The product was purified by column chromatography (SiO_2, hexane/EtOAc/MeOH 7:3:1) R_f = 0.32. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.85 (1H, bs, O*H*), 4.91 (1H, m, C*H*D), 7.29 (1H, d, J_{HH} = 8.5 Hz, Ar), 7.55 (1H, ddd, J_{HH} = 8.1 and 6.9 and 1.2 Hz, Ar), 7.68–7.77 (1H, m, Ar), 7.83 (1H, dd, J_{HH} = 8.1 and 1.5 Hz, Ar), 8.05–8.10 (1H, m, Ar), 8.15 (1H, d, J_{HH} = 8.5 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 63.9 ($t_{1:1:1}$, CD, J_{CD} = 21.96), 118.5, 126.5, 127.8, 128.8, 129.2, 130.0, 137.0, 146.8, 159.0. HRMS (TOF MS EI+): Calculated for $C_{10}H_8DNO$: Calculated 160.0747. Found 160.0754.

4.2.13. *(10-[^{2}H]-9,10-Dihydroanthracen-9-yl-10-d)-[^{2}H]-methanol (**29**).* The title compound was prepared from **15** following general procedure. An orange oil. (16.7 mg, 78 %). The product was purified by column chromatography (SiO_2, hexane/EtOAc 7:3) R_f = 0.40. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.64 (1H, dt, J_{HH} = 7.5 and 1.4 Hz, C*H*D-OH), 3.89 (1H, bs, Ar-*H*-9), 4.10 (1H, d, J_{HH} = 6.8 Hz, Ar-*H*-10), 7.21–7.28 (4H, m, Ar), 7.28–7.38 (4H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.9 (td, *C*DH-10, J_{CD} = 19.85 and 2.12 Hz), 50.1 (*C*-9), 66.2 (td, *C*DH-OH, J_{CD} = 22.20 and 4.60 Hz), 126.5, 127.0, 128.2, 128.6, 136.2, 136.6. HRMS (TOF MS EI+): Calculated for $C_{15}H_{12}D_2ONa$ 235.1068 Found 235.1060.

4.2.14. *[(3-hydroxy-[^{2}H]methyl)phenyl]ethanone (**30**).* The title compound was prepared from **16** following general procedure. A yellowih oil. (9.9 mg, 66 %). The product was purified by column chromatography (SiO_2, hexane/EtOAc/MeOH 7:3:1) R_f = 0.37. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.54–2.68 (3H, m, C*H*$_3$), 4.75 (1H, m, C*H*D), 7.47 (1H, t, J_{HH} = 7.6 Hz, Ar), 7.55–7.62 (1H, m, Ar), 7.88 (1H, dt, J_{HH} = 7.7 and 1.5 Hz, Ar), 7.93–7.98 (1H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.8, 64.6 ($t_{1:1:1}$, CD, J_{CD} = 21.59 Hz), 126.8, 127.7, 123.0, 131.7, 137.5, 141.4, 198.2. HRMS (TOF MS EI+): Calculated for $C_9H_9DO_2$ 151.0744. Found 151.0745.

4.3. General procedure for very low pressure FLP-assisted tritiation

A 1 mL round bottomed side-arm flask equipped with a magnetic stir bar was mounted onto the manifold system, evacuated to below 5×10^{-3} mbar and dried by vacuum-inert sequence. Carrier-free tritium gas (190 mbar, 2.5 Ci, 93 GBq) stored on the uranium bed was released by heating to 500 °C into reaction flask. A 0.1M solution of $B(C_6F_5)_3$ (1 mL, 100 µmol) in toluene, and 2,2,6,6-tetramethylpiperidine (18 µL, 100 µmol) was drop wise added and vigorously

stirred for 1 h at room temperature. A solution of 3-methoxybenzaldehyde (**3**) (50 µL, 1M) in toluene was added and the reaction was left react to for 2 h. The reaction solution was frozen by liquid nitrogen, residual T_2 was back-trapped on the uranium bed and the labeled alkoxyborate was hydrolyzed by addition of 1N HCl (500 µL) for 1 hour. The crude product was transported to a 50 mL flask and neutralized by addition 1 mL solution of 1M Na_2CO_3. To get rid of the labile activity, reaction mixture was lyophilized three times by H_2O-AcCN 50:50 (4 mL). The stock solution of the crude product was made by solution in 10 mL of H_2O-MeOH 40:60. The HPLC analysis showed full conversion of **3** (215 nm) and the crude radioactive yield was established at 549 mCi. Then 1/10 of the crude mixture was used for qualitative analysis. The specific activity of pure 3-methoxyphenyl-[^{3}H]-methanol (**40**) was established at 27.1 Ci/mmol following ^{1}H NMR (see Supplementary Information).

*4.3.1. 3-Methoxyphenyl-[^{3}H]-methanol (**40**).* The title compound was prepared from **3** following the general procedure. A colorless oil was obtained. Radioactive yield of pure **40** was determined at 509 mCi. Purified by HPLC, settings: Identification was done by UV detection at 245 nm and LS-radiodetector (Figure 2, middle and bottom). Column: Luna Phenylhexyl 5µ (250 mm × 10 mm). Flow: 4.7 ml/min. Eluents: (A) 99.9 % purified water, 0.1 % TFA; (B) 99.9 % acetonitrile, 0.1 % TFA. Gradient: 0–30 min, 5–40 % B, 30–35 min 40 % B, 35–45 min 60 % B. The peak of **40** was detected at 15.4 min, starting material **3** (peak at 33.2 min, Figure 2, top) was not detected in a crude mixture at all (Figure 2, middle). The labeled product **40** matches with a ^{1}H standard on an analytical HPLC (using similar gradient as for preparative HPLC). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.82 (3H, s, C*H*$_3$), 4.65 (1H, d, J_{HT} = 14.9 Hz, C*H*T), 4.77 (1H, bs, O*H*), 6.83–6.86 (1H, m, Ar), 6.92–6.95 (2H, m, Ar), 7.25–7.31 (1H, m, Ar). ^{3}H{^{1}H} NMR (320 MHz, $CDCl_3$): δ 4.65 (s, 1T, CTH). ^{3}H NMR (320 MHz, DMSO-d_6): δ 4.39 (d, 1T, *J* = 15.9 Hz, CTH). ^{3}H{^{1}H} NMR (320 MHz, $CDCl_3$): δ 4.65 (s, 1T, CTH).

Acknowledgments

The authors thank the Czech Academy of Sciences for the financial support of this project within the program RVO: 61388963. The authors declare they have no conflict of interest.

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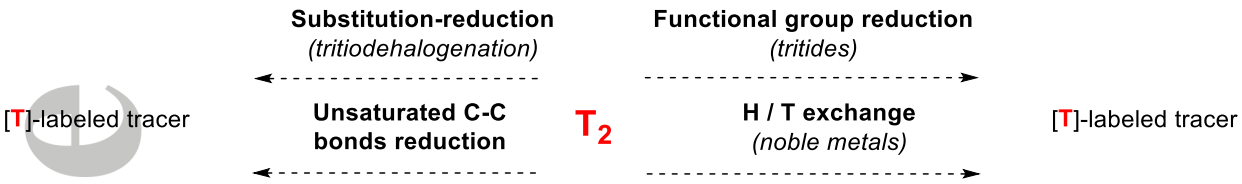


Figure 1: Common approaches for tritium labeling chemistry using carrier-free hydrogen

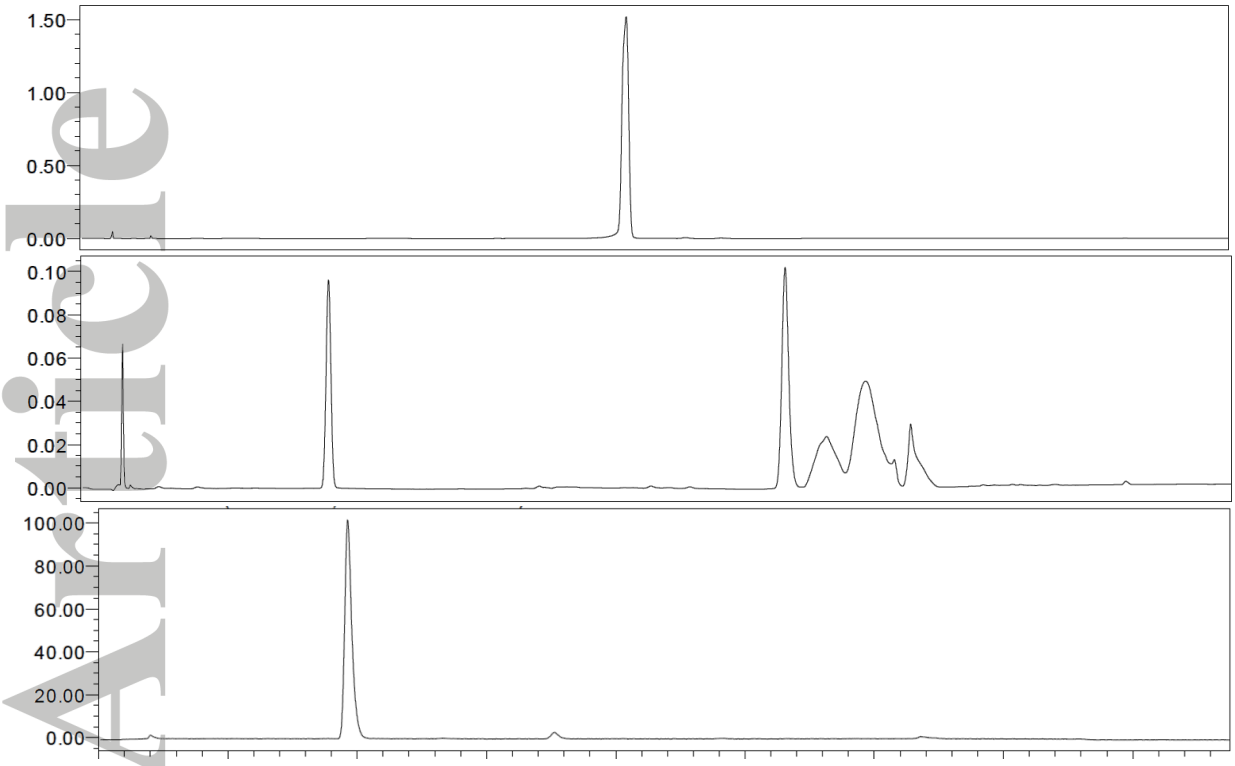
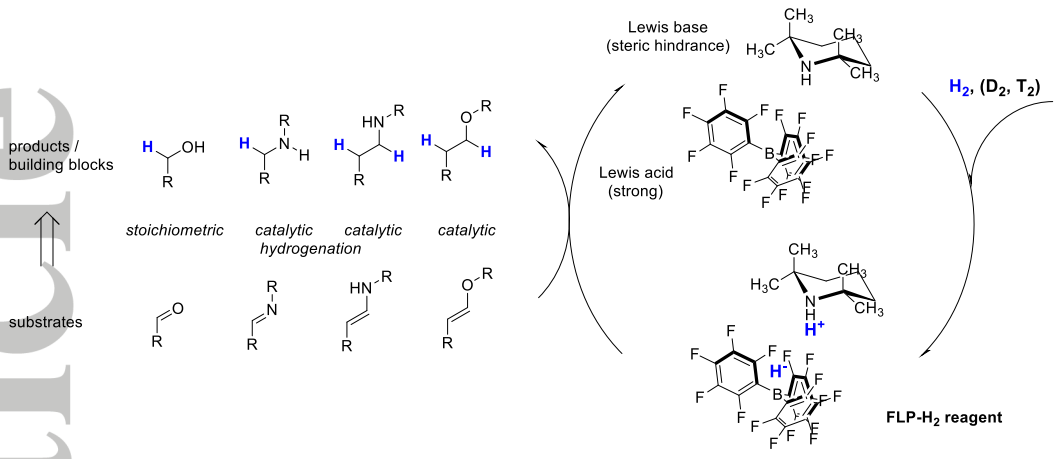
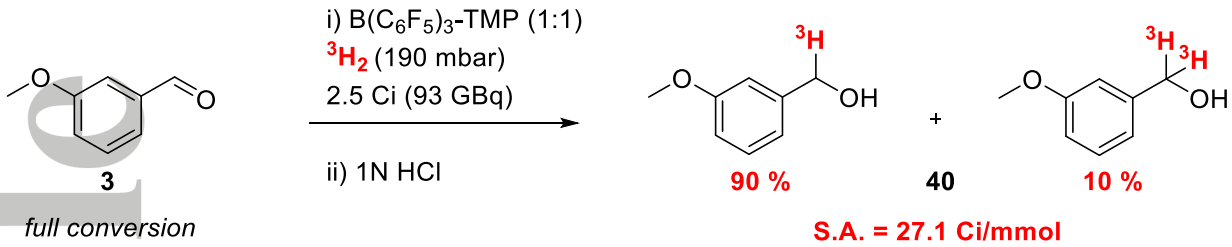


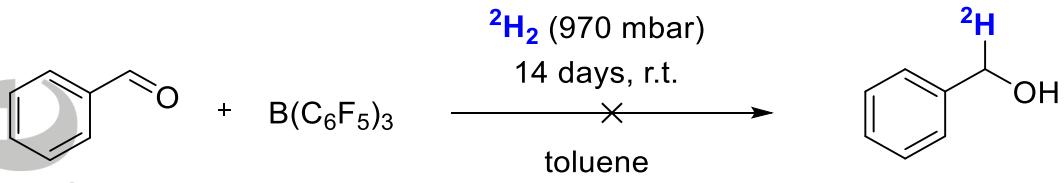
Figure 2: Analytical chromatograms after the reduction of **3** with $[B(C_6F_5)_3{}^3H][{}^3HTMP]$; top – the starting material **3** (UV 215 nm); middle –crude reaction mixture (UV 215 nm); bottom – LS-chromatogram of CRUDE reaction mixture.



Scheme 1: General mechanism for FLP-activation of hydrogen molecule and FLP-H_2 reduction of polarized double bonds

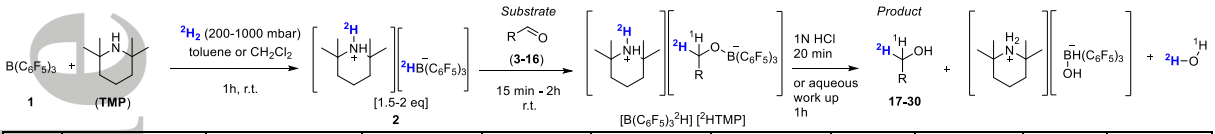


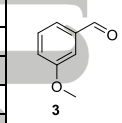
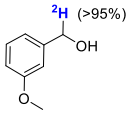
Scheme 2: FLP-assisted tritium labeling using very low pressure of hydrogen



Scheme 3: Prove of vital role of Lewis base while low pressure of hydrogen is used

Table 1: Aldehyde reduction with $[B(C_6F_5)_3{}^2H][{}^2HTMP]$ (**2**)



Entry	Substrate	Product	FLP-D_2 / Substrate	Pressure $^2H_2$ (mbar)	Lewis base	Solvent	Time (h)	Conversion (%)[a]	Isolated yield (%)	Enrichment (%)[b]
1	 3	 17	1	1000	TMP	toluene	2	74	56	>95
2			1.2	1000	TMP	toluene	2	85	67	>95
3			1.5	1000	TMP	toluene	2	99	65	>95
4			2	1000	TMP	toluene	2	99	77	>95
5			2	1000	TMP	CH_2Cl_2	2	99	75	>95
6			2	1000	TMP	MeCN	2	<5	-	-
7			2	1000	TMP	THF	2	<5	-	-
8			2	1000	(*t*Bu)$_3$P	toluene	2	<5	-	-
9			2	1000	(Mes)$_3$P	toluene	2	99	10	-
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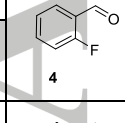
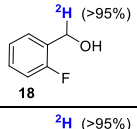
11			1.5	200	TMP	toluene	2	99	53	>95
12	 4	 18	2	1000	TMP	toluene	2	99	93	>95
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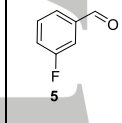
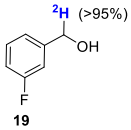
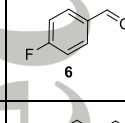
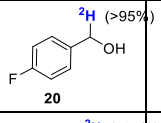
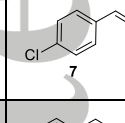
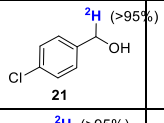
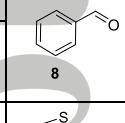
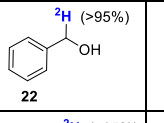
14	 5	 19	2	1000	TMP	toluene	2	99	67	>95
15	 6	 20	2	1000	TMP	toluene	2	99	79	>95
16	 7	 21	2	1000	TMP	toluene	2	99	83	>95
17	 8	 22	2	1000	TMP	toluene	2	99	93	>95
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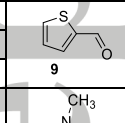
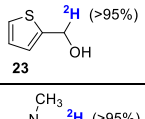
19	 9	 23	2	1000	TMP	toluene	2	99	60	>95
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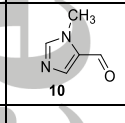
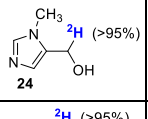
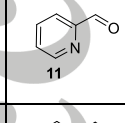
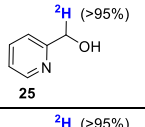
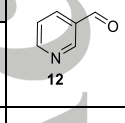
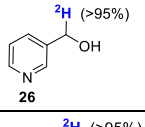
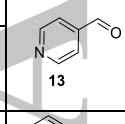
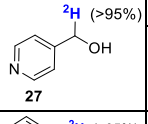
21			2	200	TMP	toluene	2	99	58	>95
22	 10	 24	2	1000	TMP	toluene	2	99	68	>95
23	 11	 25	2	1000	TMP	toluene	2	99	63	>95
24	 12	 26	2	1000	TMP	toluene	0.25	99	87	>95
25			2	200	TMP	toluene	2	99	79	
26	 13	 27	2	1000	TMP	toluene	0.25	99	81	>95
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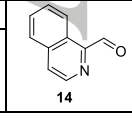
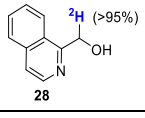
28	 14	 28	2	1000	TMP	toluene	2	99	82	>95
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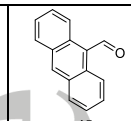
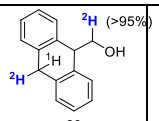
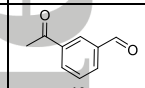
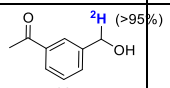
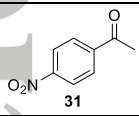
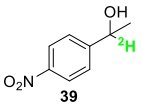
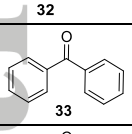
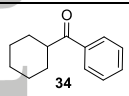
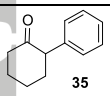
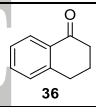
30	 15	 29	2	1000	TMP	toluene	2	99	78	>95
31	 16	 30	2	1000	TMP	toluene	2	99	66	>95

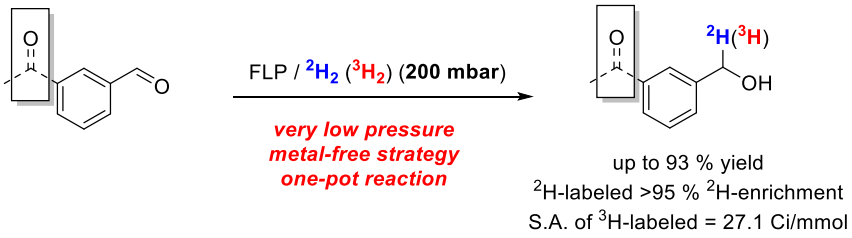
[a]All conversions were determined by ^{1}H NMR integration of the crude products. [b]Deuterium enrichment was determined by integration of labeled methylene group in ^{1}H NMR (see Supplementary Information).

Table 2: Ketone functionality treated by the reductive reagent $[B(C_6F_5)_3{}^2H][{}^2HTMP]$ (**2**)

Entry	Substrate	Product	FLP-D_2 / Substrate	Temperature (°C)	Time (h)	Conversion (%)[a]	Isolated yield (%)	Enrichment (%)[b]
1[c]	 **31**	 **39**	2	r.t.	4	53	42	>95
2[c]			3	r.t.	0.1	99	93	>95
3	 **32**	-	4		2	0	-	-
4	 **33**	-	2	r.t.	2			
5				r.t.	4			
6				80	2			
7	 **34**	-		r.t.	2			
8	 **35**	-		r.t.	2			
9	 **36**	-		r.t.	4			
10	 **37**	-		80	4			
11	 **38**	-		80	4			
12		-		r.t. [d]	17			

[a]All conversions were determined by ^1H NMR integration of the crude products. [b]Deuterium enrichment was determined by integration of labeled methylene group in ^1H NMR (see Supplementary Information). [c]Our data(47) [d]Reaction carried out in CH_2Cl_2.

Graphical Table of Contents



Reliable protocol of the routine use of frustrated Lewis pairs for reducing of polarized double bonds is reported. The described method is selective towards reduction of aldehydes and leaves unaffected non-activated ketone moieties as well as other functionalities sensitive to standard hydrogenation methods. Revolutionary is use of ultra-mild reaction conditions (200 mbar of $^{3}H_2$), non-metallic character of very selective reagent providing 94 % radiochemical purity of desired ^{3}H-labeled product in a crude reaction mixture.