Marek Ales (Orcid ID: 0000-0001-9031-8263)

Tritiodefluorination of alkyl C–F groups

Břetislav Brož [a], Aleš Marek[*]

[a] Institute of Organic Chemistry and Biochemistry, The Czech Academy of Sciences, Flemingovo n. 542/2, Prague 6, 16610, Czech Republic

A straightforward methodology of fluorine substitution by tritium/deuterium is reported. The described method is selective towards the F–C(sp^3) group and leaves both the aromatic F–C(sp^2) and F_2–C(sp^3) moieties unaffected. Alkylfluorides, readily synthesized from appropriate alcohols by treatment with diethylaminosulfur trifluoride (DAST) reagent in an overall yield up to 76 %, undergoes activation with the boron-based Lewis acid $B(C_6F_5)_3$, and stoichiometric *in situ* reduction with a tritide/deuteride reagent – the $[TMP^{2(3)}H][^{2(3)}HB(C_6F_5)_3]$ system of frustrated Lewis pair. This methodology provides an isolated yield of up to 93 % of regio-specifically labeled small organic compounds with superior ^{2}H-enrichment of over 95 %. The specific activity of prepared 1-(2-[^{3}H]-ethyl)naphthalene was determined at 29.0 Ci/mmol. The site selectivity of the Lewis acid / $[TMP^{2(3)}H][^{2(3)}HB(C_6F_5)_3]$ approach is orthogonal to currently used methods and allows for isotopic labeling of complementary positions in molecules. Reported labeling methodology proceeds well at ultra-mild reaction conditions (220 mbar of T_2), allowing very low consumption of the radioactive source (4.2 Ci/156 GBq), and producing limited amount of radioactive waste.

Keywords: tritiodefluorination, deuterodefluorination, C–F activation, frustrated Lewis pairs; hydrogen activation; tritium labeled alkane; deuterium labeled alkane; non-metallic reagent, ultra-mild reaction conditions, very low tritium pressure

[*] Corresponding author: tel. +420 220 183 395, e-mail: ales.marek@uochb.cas.cz

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1. Introduction

Tritium is the most versatile radioisotope used for identifying organic compounds in biochemical research.[1-4] Most frequently, tritiations are carried out using carrier-free tritium gas in the presence of a noble metal catalyst in order to reduce double or triple bonds,[5-9] tritiodehalogenation of appropriate synthetic precursors or to carry out $^{1}H/^{3}H$ exchanges on the desired molecule.[10-14] Catalytic dehalogenations of organic halides, using tritium gas, provide a state-of-the-art approach of site-selective labeling, while yielding high specific activity (S.A.) of the labeled material (Figure 1).[15] The advantage of this method over other available methodology is the accessibility of halogenated compounds. Aryl halides are the most common type of substrate,[10, 16-18] although halogen–C(sp^3) bonds required the activation by functionality such as carbonyl, carbonate or aryl to accelerate otherwise slow reaction.[10, 18-22] Achieved specific activities typically range between of 20–80 Ci/mmol for tritiodeiodinations, 14–25 Ci/mmol for tritiodebrominations, and 8–16 Ci/mmol for tritiodechlorinations.[10] Organic iodines and bromines undergo the reaction significantly more readily than chlorines. Since the carbon-fluorine bond is considered the strongest carbon-halide bond (bond energy of 490 kJ/mol), substrates containing C–F bonds are highly resistant to tritiolysis, and deemed unsuitable substrates.[18, 23-25] Few examples were reported on the reduction of alkylfluoride bonds, using harsh reaction conditions such as lithium powder to form organolithium compound, followed by the subsequent quenching of the reaction mixture by the addition of D_2O to finally yield deuterated heptanes.[26] Literature also reports the reduction of 4-fluoro-1,1'-biphenyl with $LiAlD_4$ catalyzed by $NbCl_5$ under reflux conditions.[27] Caputo and Stephan spectroscopically studied the fluorophilicity of the boron-based Lewis acid $B(C_6F_5)_3$ in the activation of a series of alkyl fluorides.[28, 29] Stoichiometric reaction of $B(C_6F_5)_3$ / alkyl fluoride with the salt $[t\mathrm{Bu_3P^1H}][^1\mathrm{HB}(C_6F_5)_3]$, yielded partial conversion of both studied substrates, 1-fluoropentane and 1-fluoroadamantane, producing pentane and adamantane respectively.

In our own work, we have utilized a borane-based Lewis acid $B(C_6F_5)_3$ to generate the corresponding frustrated Lewis pair (FLP) with a sterically demanding amine (2,2,6,6-tetramethylpiperidine, TMP), under atmosphere of deuterium/tritium gas, to form $[\mathrm{TMP}^{2(3)}\mathrm{H}][^{2(3)}\mathrm{HB}(C_6F_5)_3]$.[30] The salt FLP-$^2H_2$ was efficiently used for the direct reduction of carbonyl compounds, yielding alcohols with both high ^2H-enrichment (>95 %) and high isolated yields (up to 97 %). We have also illustrated the ability of FLP to carried out the splitting of tritium molecule (^3H–^3H bond dissociation energy 446.9 kJ/mol) under very mild reaction conditions – (505 mbar of $^3H_2$, r.t., 1h).[30] The reagent $[\mathrm{TMP}^3\mathrm{H}][^3\mathrm{HB}(C_6F_5)_3]$ was further successfully employed for the reduction of p-(*N*-Boc)-benzaldehyde to produce p-(*N*-Boc)-aminophenyl-[^3H]-methanol isolated in an excellent yield (367 mCi) and S.A. of 24.3 Ci/mmol. Recently, we have further reduce consumption of tritium gas as the FLP-assisted reduction of carbonyl compound was successfully carried out at 190 mbar of T_2 (2.5 Ci, 93 GBq), providing tritium labeled alcohol 3-methoxyphenyl-[^3H]-methanol with S.A. of 27.1 Ci/mmol.[31] It is noteworthy an outstanding selectivity of FLP-^3H reagent at reduction of carbonyl compounds providing 94 % radiochemical purity of desired crude product.

Our research, as well as other contributors in literature, have demonstrated the unique reactivity of FLPs in the activation of molecule of deuterium for the heterolytic cleavage of ^2H–^2H molecule (bond dissociation energy 443.4 kJ/mol).[32-34] We are

continuously developing new FLP applications for hydrogen labeling transformations. Herein, we investigate the fluorophilicity of Lewis acid $B(C_6F_5)_3$ in the activation of C–F bonds for the stoichiometric reaction with $[TMP^{2(3)}H][^{2(3)}HB(C_6F_5)_3]$.

2. Results and discussion

To reach maximal defluorination-labeling conversion power of the complex system of $B(C_6F_5)_3$ and FLP-$^2H_2$, as a source of deuteride, we decided to use a ratio of Lewis acid : Lewis base : fluorinated derivatives of 3:2:1 in dry CH_2Cl_2 under an atmosphere of $^2H_2$. Although Caputo stated that a ratio of 2:1:1 leads to the full conversion of their chosen fluoroalkanes in an NMR-tube-experiment study; it is noteworthy that based on their depicted ^1H spectra they have reach a conversion of below 50 % for 1-fluoropentane (no data in terms of the conversion nor the reaction time were further provided).[28] Achieving a full conversion of starting material remains an imperative, since we are seeking a preparative scale of this reaction. Based on our experience with the reactivity of FLP-$^2H_2$ reagents used for reduction of polarized double bonds, there is a need for the use of 1.5–2.0 eq of this reagent to reach full conversion of reduced material unless the substrate is activated by electron withdrawing group.[30] Monofluorinated compounds 1-fluorotetradecane ([F]-**1**), 1-fluoroadamantane ([F]-**2**), 3-fluoro-1-phenylpropane ([F]-**3**) and 1-(2-fluoroethyl)naphthalene ([F]-**4**), provided in all cases the desired ^2H-labeled derivatives [^2H]-(**1–4**) with high isolated yield (75–93 %) and excellent ^2H-enrichment (>95 %, determined by ^1H NMR) after a short period of time (Scheme 1). Reaction conditions were optimized with use of 1-fluorotetradecane ([F]-**1**); after 2 hours of reaction time a conversion of 90 % was achieved, and after 4 hours of reaction time a full conversion of alkylfluoride [F]-**1** was witnessed. No other byproduct was detected in the crude reaction mixture by ^1H NMR. To ensure the full conversion of alkylfluorides, our experiments were allowed to react overnight. The reaction course was followed by measurement of NMR spectra, where the characteristic signals were found to be absent. For instance, for 1-fluorotetradecane ([F]-**1**) the characteristic signal for the CH_2F moiety in ^1H spectra at 4.43 ppm (2H, *dt*, $^2J_{F,H}$ = 47.3 Hz and $^3J_{H,H}$ = 6.2 Hz) as well as the multiplet of FCH_2CH_2 at 1.77–1.60 ppm were found to be absent. In the ^{13}C NMR spectra the disappearance of the doublets at 84.4 ppm ($^1J_{F,C}$ = 164 Hz, FCH_2), 30.6 ppm ($^2J_{F,C}$ = 19.4 Hz, FCH_2CH_2), and 25.3 ppm ($^3J_{F,C}$ = 5.5 Hz, $FCH_2CH_2CH_2$) were witnessed. The deuterium incorporation in the product [^2H]-**1** was unambiguously confirmed showing the characteristic 1:1:1 triplet at 14.0 ppm ($J_{C,D}$ = 19.2 Hz, DCH_2). For the detailed procedure, spectra and full characterization of the isolated ^2H-labeled products, as well as the corresponding synthetic precursor see the Supplementary Information section. In the reaction between FLP-$^2H_2$ and 1-fluorotetradecane ([F]-**1**), where a ratio of 2:1 were used, and no additional $B(C_6F_5)_3$ were added for the activation of the C–F bond, no conversion of this fluoroalkane were witnessed after 20 hours of reaction time. To emphasize the applicability of this complementary labeling concept, we decided to test 1-fluorotetradecane as a model substrate under the reaction conditions used as a golden standard for hydrogendehalogenations – substrate / [Pd/C; 30 %] (1 eq, w/w) / Et_3N (6 eq) / EtOAc / $^2H_2$ (1.5 bar) – over prolonged period of time of 48 hours. As was expected, no conversion of this alkyl fluoride was detected. It is noteworthy to underline the selectivity and mildness of FLP-$^2H_2$ reagents since the reagent tolerates most of the frequent functional groups such as nitro, methoxy, silylethers, *N*-Boc, *N*-Bn,

trialkylamines, C(sp^2)-halogens, (hetero)arenes, non-activated ketons, sulfonamides, ester functionalities, ferrocenes, zirconocenes, etc.[30, 35-38]

The secondary carbon F–C(sp^3) moiety employed for C–F analogous activation showed elimination of the HF leading to olefin formation as a major product (see Supplementary Information) of reaction (80 % yield). Full conversion of 3-fluoro-1,5-diphenylpentane ([F]-**5**) was observed and the desired ^{2}H-labeled 3-[^{2}H]-1,5-diphenylpentane ([^{2}H]-**5**) was isolated in 20 % yield with ^{2}H-enrichment over 95 %.

On the other hand, attempts to carry out C–F activation in both polyfluorinated alkanes (such as the F_2–C(sp^3) moiety [F]-**6**) synthesized using the DAST reagent and carbonyl compound; see Supplementary Information) and fluoroarenes (the F–C(sp^2) moiety [F]-**7**) turned out to be fruitless even after prolonged reaction time up to 140 hours (Scheme 2). No C–F activation was achieved with commercially available Betamethasone ([F]-**8**) bearing sterically very demanding fluorine group on the C-9 position. The methylation of OH groups, to support the solubility of such otherwise polar substrate in reaction medium, had no increase in the reactivity and was thus not of any help.

Except for 1-fluorotetradecane ([F]-**1**), 1-fluoroadamantane ([F]-**2**) and Betamethasone ([F]-**8**) all other alkylfluorides [F]-(**3–7**), used in this work, were prepared from the appropriate alkylalcohols or aldehydes and their treatment with diethylaminosulfur trifluoride (DAST) reagent in CH_2Cl_2 at 0°C.[39, 40] Overall yield up to 76 % were obtained (see Supplementary Information).

The successful isolation of the series of deuterium-labeled alkanes [^{2}H]-(**1–5**) was encouraging for the application of this procedure analogically for the tritium experiment. The ability of FLP to activate tritium molecules under subatmospherical pressure of carrier-free tritium gas (505 mbar), producing [$B(C_6F_5)_3{}^3H$][^{3}HTMP] was proved recently.[30] 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 (220 mbar, 4.2 Ci, 156 GBq). To ensure full conversion of fluorinated precursor [F]-**4** in short period of reaction time (2 h), we decided to increase the ratio of Lewis acid : Lewis base : fluorinated substrate to 6:4:1 (Scheme 3). A solution of 1-(2-fluoroethyl)naphthalene ([F]-**4**, 2.6 mg) in dry DCM was used as substrate to prove ability of borane/FLP-^{3}H reagent to substitute fluorine atom in [F]-**4** by tritium. After two hours of reaction, a crude product was lyophilized and subjected to flash column chromatography providing desired tritium labeled alkane [^{3}H]-**4** [100.8 mCi (3.72 GBq)]. Full conversion of [F]-**4** was achieved according to ^{1}H NMR of [^{3}H]-**4** as characteristic signals of substrate [F]-**4** completely disappeared (Figure 4.15.2 in Supplementary Information, the bottom spectrum). The structure of desired product [^{3}H]-**4** was unequivocally identified by ^{3}H, ^{1}H NMR, and HR-MS spectrometry. The chemical shift of ^{3}H signal at 1.38 ppm in the CH_2CH_2T moiety is identical to CH_2CH_2H of ^{1}H-standard, as well as to CH_2CH_2D of ([^{2}H]-**4**). Characteristic tritium signal in the ^{3}H-^{1}H coupled spectrum is split to a triplet of triplets ($^2J_{T,H}$ = 13.8 Hz, $^3J_{T,H}$ = 8.0 Hz). Specific activity (S.A.) of [^{3}H]-**4** was calculated based on the HR-MS spectrum (Figure 4.15.3 in Supplementary Information, the bottom spectrum) at 29.0 Ci/mmol (1.07 TBq/mmol). The measured signal of desired product [^{3}H]-**4** perfectly matches with its simulation (calculated 158.1021 Da, found 158.1020 Da), and no un-labeled product was detected ($C_{12}H_{12}$, M = 156.0939 Da).

The outstanding S.A. (precisely one tritium per labeled position) was reached due to a different mechanism employed in reported methodology compare to traditional hydrogen dehalogenations catalyzed by [Pd^0] initiation of oxidative addition among C-halogen bond (Figure 1) under atmosphere of hydrogen gas, ending up with reductive elimination. Increasing aryl C-halogen bond dissociation energies in the order I (223 kJ/mol) < Br (281 kJ/mol) < Cl (340 kJ/mol) < F (453 kJ/mol), combined with an increasing halogens electronegativities I < Br < Cl < F, ends up with a trend of measured dehalogenation rates of different halo group in the order I >> Br > Cl, fluorine leaving as an unsuitable substrate.[10] Here the mechanism is based on the substitution of fluorine by hydrogen. The particular C–F bond is significantly weakened by interaction with a strong lewis acid such as $B(C_6F_5)_3$, which makes possible substitution of fluorine by deuteride/tritide delivered in this case by a FLP-$^{2(3)}$H reagent.

3. Conclusion

As a proof-of-concept, we reported a detailed study of site-specific deuterium-labeled alkanes by employing C–F activation of 1°, 2° and 3° alkyl fluorides as a complementary tool to existing deuterium labeling methods. Our intention was to design a synthetic protocol applicable for tritium labeling of special candidates where one or more C–F moieties could be selectively and efficiently used for site specific late stage labeling. Successful labeling of 1-(2-[^{3}H]-ethyl)naphthalene using reported strategy under very mild reaction conditions offers a synthetic protocol generally applicable for smooth tritium labeling of organic compounds yielding radio tracers with maximal achievable specific activity per labeled bond. Ultra mild reaction conditions, non-metallic character of reagent, commercial availability of reagents, proven excellent selectivity, very high yield and full conversion of proper substrates, synthetically readily available monofluorinated substrates, and unambiguous selectivity towards various C–F moieties paved the way for use of this concept as a complementary tool for tritium labeling experiments of applicable substrates.

4. Experimental section

General

The ^{1}H/^{3}H-, ^{13}C- and ^{19}F-NMR spectra were recorded at 300/320, 400 or 600 MHz; 75, 100 or 150 MHz and 377 or 470 MHz with a Bruker Avance II 300 MHz, Avance III™ HD 400 MHz or Avance III™ HD 600 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). Liquid scintillation measurements were done on a PerkineElmer TriCarb 2900 liquid

scintillation counter (LSC) in a Rotiszint Eco+ cocktail. $B(C_6F_5)_3$, Betamethasone and 1-fluorotetradecane were purchased from TCI Europe N.V.. 2,2,6,6-Tetramethylpiperidine and 1-fluoroadamantane were purchased from Fluorochem Ltd..

4.1 Generation of the Lewis acid / FLP-$^2H_2$ reagent

A well-dried 3-mL deuteration flask was filled with deuterium gas (1200 mbar) at room temperature and then, the 0.1M solution of $B(C_6F_5)_3$ in dry CH_2Cl_2 (200 μmol, 3 eq.), and neat TMP (133 μmol, 2 eq.), were added consecutively. After stirring the reaction mixture for 1 hour, the Lewis acid / FLP-$^2H_2$ reagent was prepared, and used in the next step of reaction sequence. For details see SI (GP–2).

4.2 General procedure for the activation of fluoride substrates

The appropriate alkyl fluoride [F]-(**1–5**) (67 μmol, 1 eq.) in dry CH_2Cl_2 (350 μL), was added to the freshly prepared Lewis acid / FLP-$^2H_2$ reagent. The reaction mixture was vigorously stirred and allowed to react overnight at room temperature. The mixture was then diluted by water (2 mL) and product extracted by addition of CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried by $MgSO_4$ and solvent was evaporated. The crude product was purified by short column (*n*-hexane or CH_2Cl_2, silica gel 60, column 7×Ø1.5 cm, 20 mL of mobile phase) to get rid of polar reagents. After evaporation of solvent, the corresponding pure deutero-alkanes [^{2}H]-(**1–5**) were isolated. See SI (GP–3) for details.

4.2.1 The synthesis of 1-[^{2}H]-tetradecane ([^{2}H]-1).

Derivative [^{2}H]-**1** was prepared from 1-fluorotetradecane ([F]-**1**) (14.5 mg, 67 μmol) using the general procedure, and was isolated as colourless oil (12.4 mg, 93 % yield). ^{1}H NMR ($CDCl_3$, 400.1 MHz) δ (ppm) : 1.39–1.19 (24H, m, 12×CH_2), 0.95–0.80 (5H, m, CH_3 + CH_2D). ^{13}C NMR (100.8 MHz, $CDCl_3$) δ (ppm): 32.09, 32.07, 29.9, 29.8, 29.7, 29.5, 22.9, 22.8, 14.3, 14.0 ($t_{1:1:1}$, J_{CD} = 19.1 Hz). EI-HRMS: For $C_{14}H_{29}D^+$ $[M]^+$ calcd. 199.2410 Da, found 199.2414 Da.

4.2.2 The synthesis of 1-[^{2}H]-adamantane ([^{2}H]-2).

The desired deuterated [^{2}H]-**2** was prepared from 1-fluoroadamantane ([F]-**2**) (10.3 mg, 67 μmol) using the general procedure after 4 hours of reaction, and was isolated as a colourless oil (7.2 mg, 78 % yield). ^{1}H NMR ($CDCl_3$, 400.1 MHz) δ (ppm) : 1.94–1.86 (3H, m, 3×C*H*), 1.82–1.72 (12H, m, 6×CH_2). ^{13}C NMR (100.8 MHz, $CDCl_3$) δ (ppm): 37.8, 37.6, 28.3, 27.8 ($t_{1:1:1}$, J_{CD} = 20.1 Hz). EI-HRMS: For $C_{10}H_{15}D^+$ $[M]^+$ calcd. 137.1317 Da, found 137.1315 Da.

4.2.3 The synthesis of 1-[^{2}H]-3-phenylpropane ([^{2}H]-3).

Derivative [^{2}H]-**3** was prepared from 1-fluoro-3-phenylpropane ([F]-**3**) using general procedure. Due to volatility of **3**, product was isolated and characterized in a CH_2Cl_2 solution and the isolated yield could not be determined. A spectral characterization is in accordance with those described in literature.[41] The deuterium incorporation was unambiguously confirmed by signals showing characteristic H–D splitting constants for C*H*$_2$CH$_2$D and CH$_2$C*H*$_2$D in ^{1}H NMR and C–D splitting constants for *C*H$_2$D in ^{13}C NMR. ^{1}H NMR ($CDCl_3$, 400.1 MHz) δ (ppm) : δ 7.31–7.25 (2H, m, Ar*H*), 7.20–7.16 (3H, m, Ar*H*), 2.62–2.56 (2H, m, ArC*H*$_2$), 1.64 (2H, pt$_{1:1:1}$, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,D}$ = 1.1 Hz, C*H*$_2$CH$_2$D), 0.93 (2H, tt$_{1:1:1}$, $^3J_{H,H}$ = 7.4 Hz, $^2J_{H,D}$ = 2.0 Hz, CH$_2$C*H*$_2$D). ^{13}C NMR ($CDCl_3$, 100.8 MHz) δ (ppm) : 142.8, 128.6, 128.3, 125.7, 38.2, 24.6, 13.6 (t$_{1:1:1}$, $J_{C,D}$ = 19.1 Hz). EI-HRMS: For $C_{12}H_{11}D^+$ $[M]^+$ calcd. 121.1002 Da, found 121.1006 Da.

4.2.4 The synthesis of 1-(2-[^{2}H]-ethyl)naphthalene ([^{2}H]-4).

Derivative [^{2}H]-**4** was prepared from 1-(2-fluoroethyl)naphthalene ([F]-**4**) (11.7 mg, 67 μmol) using the general procedure, and was isolated as colourless oil (9.5 mg, 90 % yield). ^{1}H NMR ($CDCl_3$, 400.1 MHz) δ (ppm) : 8.10–8.05 (1H, m, Ar*H*), 7.89–7.84 (1H, m, Ar*H*), 7.72 (1H, d, $^3J_{H,H}$ = 8.1 Hz, ArH), 7.55–7.45 (2H, m, 2× Ar*H*), 7.45–7.39 (1H, m, Ar*H*), 7.37–7.33 (1H, m, Ar*H*), 3.13 (2H, t, *J* = 7.4 Hz, C*H*$_2$CH$_2$D), 1.38 (tt$_{1:1:1}$, $^3J_{H,H}$ = 7.5 Hz, $^2J_{H,D}$ = 2.0 Hz, 2H, CH$_2$C*H*$_2$D). ^{13}C NMR ($CDCl_3$, 100.8 MHz) δ (ppm) : 140.4, 134.0, 131.9, 128.9, 126.5, 125.8, 125.5, 125.0, 123.9, 26.0, 14.9 (t$_{1:1:1}$, $J_{C,D}$ = 19.5 Hz). EI-HRMS: For $C_{12}H_{11}D^+$ $[M]^+$ calcd. 157.1002 Da, found 157.1003 Da.

4.2.5 The synthesis of 1,5-diphenyl-3-[^{2}H]-pentane ([^{2}H]-5).

The desired deuterated [^{2}H]-**5** was prepared from 1,5-diphenyl-3-fluoro-pentane ([F]-**5**) (13.8 mg, 67 μmol) using the general procedure, and was isolated as a minor product (2.9 mg, 20 %). Oily product was identified by HRMS: EI-HRMS: For $C_{17}H_{19}D^+$ $[M]^+$ calcd. 225.1628 Da, found 225.1629 Da.

4.3 The synthesis of 1-(2-[^{3}H]-ethyl)naphthalene ([^{3}H]-4).

Two-neck 1.4-mL hydrogenation flask equipped with a magnetic stir bar and septum was mounted onto a tritiation manifold system. The flask was well dried by vacuum-inert sequence, and a carrier-free tritium gas (220 mbar, 4.2 Ci/156 GBq) was released into the flask. Subsequently, 0.1M $B(C_6F_5)_3$ solution in dry DCM (0.9 mL, 90 μmol, 6 eq.) and 2,2,6,6-tetramethylpiperidin (10 μL, 8.4 mg, 60 μmol, 4 eq.) were added consecutively *via* syringe and the reaction mixture was vigorously stirred for 1 hour. A solution of 1-(2-fluoroethyl)naphthalene ([F]-**4**, 2.6 mg, 15 μmol, 1 eq.) in dry DCM (250 μL) was injected, and the mixture was stirred for additional 2 hours. The reaction mixture was then frozen by liquid nitrogen and an excessive tritium was back-trapped on a uranium bed. The reaction mixture was filtered through a 0.22 μm PTFE syringe filter, and the reaction flask was rinsed with methanol/water 2:1 mixture (5 × 0.8 mL) and with 1M aqueous HCl (0.5 mL). To remove a labile activity, the crude product was

repeatedly lyophilized by methanol/water 4:1 mixture (5 mL). The crude product was dissolved in DCM (1.5 mL), and purified by flash column chromatography (DCM, silica gel, column 10 cm × Ø1.2 cm, 20 mL of mobile phase). It was isolated 100.8 mCi (3.72 GBq) of pure [^{3}H]-**4**. The desired product [^{3}H]-**4** was identified by ^{3}H and ^{1}H NMR spectrometry as well as by MS (Supplementary Information, 4.15). Specific activity$_{(MS)}$ was determined of 29.0 Ci/mmol (1.07 TBq/mmol).

^{3}H NMR ($CDCl_3$, 320.1 MHz) δ (ppm) : 1.38 (1[^{3}H], tt, $^2J_{T,H}$ = 13.8 Hz, $^3J_{T,H}$ = 8.0 Hz, $CH_2CH_2{}^3H$). ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ (ppm) : 8.06 (1H, d, $^3J_{H,H}$ = 8.0 Hz, Ar*H*), 7.90 – 7.82 (1H, m, Ar*H*), 7.71 (1H, d, $^3J_{H,H}$ = 8.2 Hz, 1H), 7.57 – 7.31 (4H, m, 4×Ar*H*), 3.11 (2H, q, $^3J_{H,H/T}$ = 7.7 Hz, $CH_2CH_2{}^3H$). ^{1}H signal of $CH_2CH_2{}^3H$ detected at 1.38 ppm gets partially overlapped by grease used at lyophilization and was not integrated. EI-HRMS: For $C_{12}H_{11}T^+$ $[M]^+$ calcd. 158.1021 Da, found 158.1020 Da.

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References

1. Graham Lappin ST. Radiotracers in Drug Development. Boca Raton CRC Press 2006. 320 p.
2. Lockley WJS, McEwen A, Cooke R. Tritium: a coming of age for drug discovery and development ADME studies. J Label Compd Radiopharm. 2012;55(7):235-57.
3. Atzrodt J, Derdau V, Kerr WJ, Reid M. Deuterium- and Tritium-Labelled Compounds: Applications in the Life Sciences. Angew Chem-Int Edit. 2018;57(7):1758-84.
4. Yu RP, Hesk D, Rivera N, Pelczer I, Chirik PJ. Iron-catalysed tritiation of pharmaceuticals. Nature. 2016;529(7585):195-9.
5. Di Giglio MG, Muttenthaler M, Harpsoe K, Liutkeviciute Z, Keov P, Eder T, et al. Development of a human vasopressin V-1a-receptor antagonist from an evolutionary-related insect neuropeptide. Scientific Reports. 2017;7:15.
6. Tran PT, Larsen CO, Rondbjerg T, De Foresta M, Kunze MBA, Marek A, et al. Diversity-Oriented Peptide Stapling: A Third Generation Copper-Catalysed Azide-Alkyne Cycloaddition Stapling and Functionalisation Strategy. Chem-Eur J. 2017;23(14):3490-5.
7. Marek A, Patil MR, Elbert T. The labeling of brassinosteroids by tritium. RSC Adv. 2015;5(80):65214-20.
8. Al-Khawaja A, Haugaard AS, Marek A, Loffler R, Thiesen L, Santiveri M, et al. Pharmacological Characterization of H-3 ATPCA as a Substrate for Studying the Functional Role of the Betaine/GABA Transporter 1 and the Creatine Transporter. ACS Chem Neurosci. 2018;9(3):545-54.
9. Marek A, Pedersen MHF, Vogensen SB, Clausen RP, Frolund B, Elbert T. The labeling of unsaturated gamma-hydroxybutyric acid by heavy isotopes of hydrogen: iridium complex-mediated H/D exchange by C-H bond activation vs reduction by boro-deuterides/tritides. J Label Compd Radiopharm. 2016;59(12):476-83.
10. Voges R, Heys JR, Moenius T. Preparation of compounds labeled with tritium and carbon-14: John Wiley & Sons; 2009.
11. Lockley WJS. 30 Years with ortho-directed hydrogen isotope exchange labelling. J Label Compd Radiopharm. 2007;50(9-10):779-88.
12. Lockley WJS, Heys JR. Metal-catalysed hydrogen isotope exchange labelling: a brief overview. J Label Compd Radiopharm. 2010;53(11-12):635-44.
13. Loh YY, Nagao K, Hoover AJ, Hesk D, Rivera NR, Colletti SL, et al. Photoredox-catalyzed deuteration and tritiation of pharmaceutical compounds. Science. 2017;358(6367):1182-+.
14. Atzrodt J, Derdau V, Kerr WJ, Reid M. C-H Functionalisation for Hydrogen Isotope Exchange. Angew Chem-Int Edit. 2018;57(12):3022-47.
15. Saljoughian M. Synthetic tritium labeling: Reagents and methodologies. Synthesis-Stuttgart. 2002(13):1781-801.
16. Alcaide A, Marconi L, Marek A, Haym I, Nielsen B, Mollerud S, et al. Synthesis and pharmacological characterization of the selective GluK1 radioligand (S)-2-amino-3-(6 3H -2,4-dioxo-3,4-dihydrothieno.3,2-d pyrimidin1.2H)- yl) propanoic acid (H-3 -NF608). Medchemcomm. 2016;7(11):2136-44.
17. Kuhne S, Nohr AC, Marek A, Elbert T, Klein AB, Brauner-Osborne H, et al. Radiosynthesis and characterisation of a potent and selective GPR139 agonist radioligand. RSC Adv. 2016;6(2):947-52.
18. Pinder AR. The Hydrogenolysis of Organic Halides. Synthesis. 1980(6):425−52.

19. Marek A, Patil MR, Klepetarova B, Kohout L, Elbert T. A stereospecific pathway for the introduction of deuterium on the brassinosteroid skeleton by reductive dechlorination of chlorocarbonates. Tetrahedron Letters. 2012;53(16):2048-50.
20. Marek A, Klepetarova B, Elbert T. A facile method for steroid labeling by heavy isotopes of hydrogen. Tetrahedron. 2015;71(29):4874-82.
21. Elbert T, Patil MR, Marek A. Enantiospecific tritium labeling of 28-homocastasterone. J Label Compd Radiopharm. 2017;60(3):176-82.
22. Oklestkova J, Tarkowska D, Eyer L, Elbert T, Marek A, Smrzova Z, et al. Immunoaffinity chromatography combined with tandem mass spectrometry: A new tool for the selective capture and analysis of brassinosteroid plant hormones. Talanta. 2017;170:432-40.
23. Shen Q, Huang Y-G, Liu C, Xiao J-C, Chen Q-Y, Guo Y. Review of recent advances in CF bond activation of aliphatic fluorides. J Fluor Chem. 2015;179:14-22.
24. Burdeniuc J, Jedlicka B, Crabtree RH. Recent advances in C-F bond activation. Chem Ber-Recl. 1997;130(2):145-54.
25. Amii H, Uneyama K. C-F Bond Activation in Organic Synthesis. Chem Rev. 2009;109(5):2119-83.
26. Guijarro D, Martínez P, Yus M. Reductive defluorination of fluoroalkanes. Tetrahedron. 2003;59(8):1237-44.
27. Fuchibe K, Ohshima Y, Mitomi K, Akiyama T. Hydrodefluorinations by low-valent niobium catalyst. J Fluor Chem. 2007;128(10):1158−67.
28. Caputo CB, Stephan DW. Activation of Alkyl C-F Bonds by $B(C_6F_5)_3$: Stoichiometric and Catalytic Transformations. Organometallics. 2012;31(1):27−30.
29. Caputo CB, Hounjet LJ, Dobrovetsky R, Stephan DW. Lewis Acidity of Organofluorophosphonium Salts: Hydrodefluorination by a Saturated Acceptor. Science. 2013;341(6152):1374-7.
30. Marek A, Pedersen MHF. Frustrated Lewis pairs-assisted reduction of carbonyl compounds. Tetrahedron. 2015;71(6):917-21.
31. Doubkova S, Marek A. Frustrated Lewis pairs: A real alternative to deuteride / tritide reductions. Journal of Labelled Compounds and Radiopharmaceuticals. 2019, doi: 10.1002/jlcr.3774.
32. Eros G, Nagy K, Mehdi H, Papai I, Nagy P, Kiraly P, et al. Catalytic Hydrogenation with Frustrated Lewis Pairs: Selectivity Achieved by Size-Exclusion Design of Lewis Acids. Chem-Eur J. 2012;18(2):574-85.
33. Ozgun T, Bergander K, Liu L, Daniliuc CG, Grimme S, Kehr G, et al. A Frustrated Phosphane-Borane Lewis Pair and Hydrogen: A Kinetics Study. Chem-Eur J. 2016;22(34):11958-61.
34. Tussing S, Greb L, Tamke S, Schirmer B, Muhle-Goll C, Luy B, et al. Autoinduced Catalysis and Inverse Equilibrium Isotope Effect in the Frustrated Lewis Pair Catalyzed Hydrogenation of Imines. Chem-Eur J. 2015;21(22):8056-9.
35. Stephan DW. Frustrated Lewis Pairs: From Concept to Catalysis. Accounts Chem Res. 2015;48(2):306-16.
36. Stephan DW, Erker G. Frustrated Lewis Pairs: Metal-free Hydrogen Activation and More. Angew Chem-Int Edit. 2010;49(1):46-76.
37. Stephan DW. "Frustrated Lewis pair" hydrogenations. Org Biomol Chem. 2012;10(30):5740-6.
38. Stephan DW, Greenberg S, Graham TW, Chase P, Hastie JJ, Geier SJ, et al. Metal-Free Catalytic Hydrogenation of Polar Substrates by Frustrated Lewis Pairs. Inorg Chem. 2011;50(24):12338-48.

39. von Halasz SP, Glemser O. Darstellung neuer Aminoschwefelmonofluoridimide und -oxidmonofluoridimide sowie über die Struktur der Aminoschwefeloxidtrifluoride. Chem Ber. 1970;103:594−602.
40. Middleton WJ. New Fluorinating Reagents. Dialkylaminosulfur Fluorides. J Org Chem. 1975;40(5):574−8.
41. Espinal-Viguri M, Neale S, Coles NT, Macgregor SA, Webster RL. Room temperature iron-catalyzed transfer hydrogenation and regioselective deuteration of carbon-carbon double bonds. J Am Chem Soc. 2019;141(1):572−82.

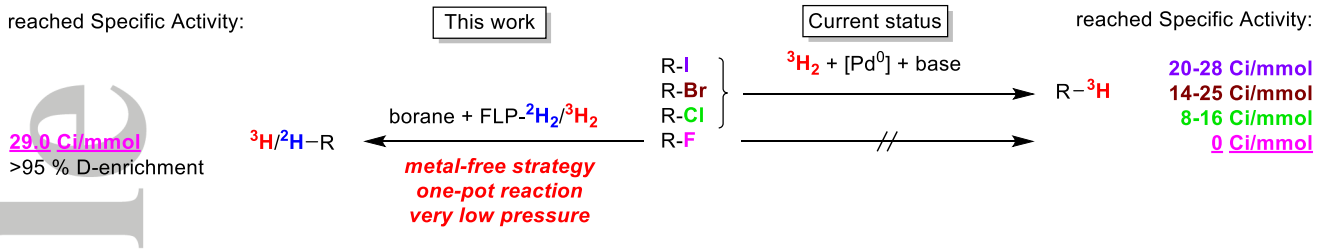
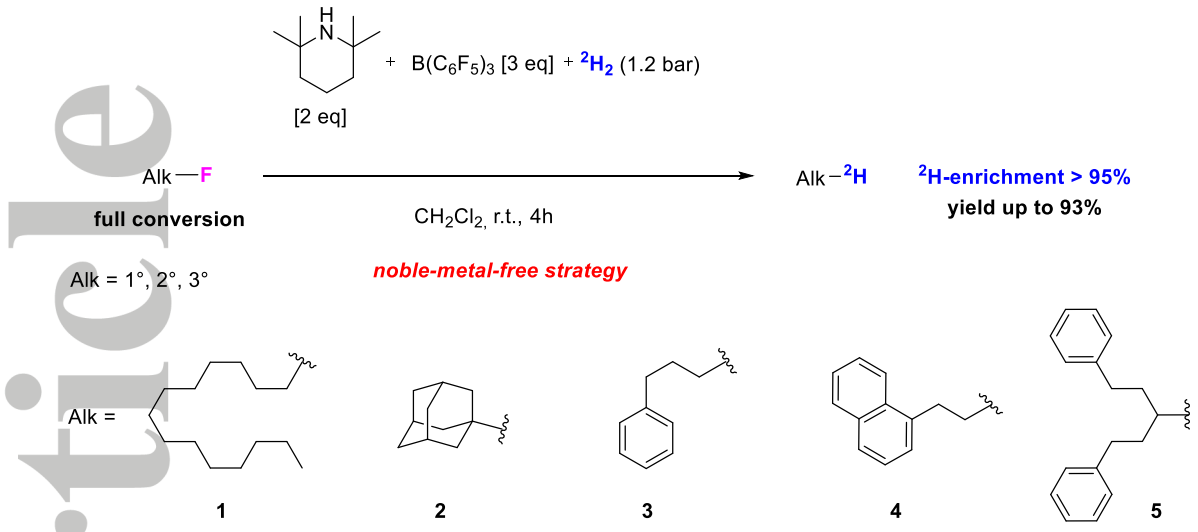
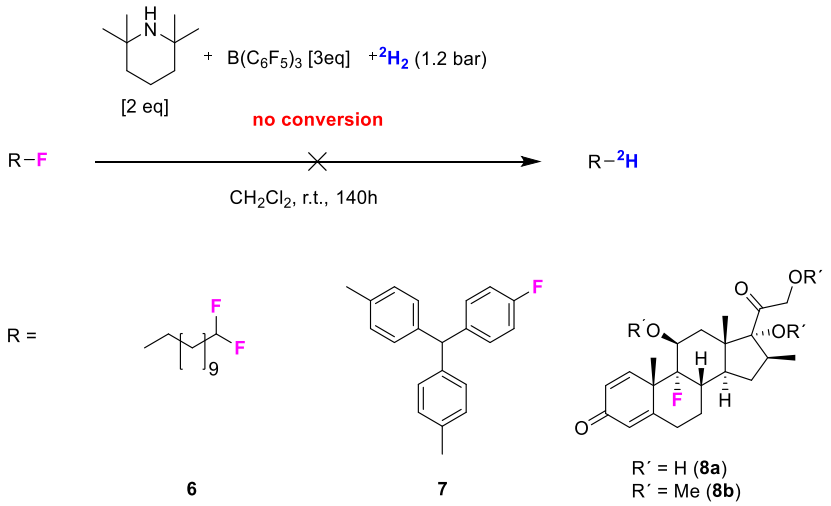


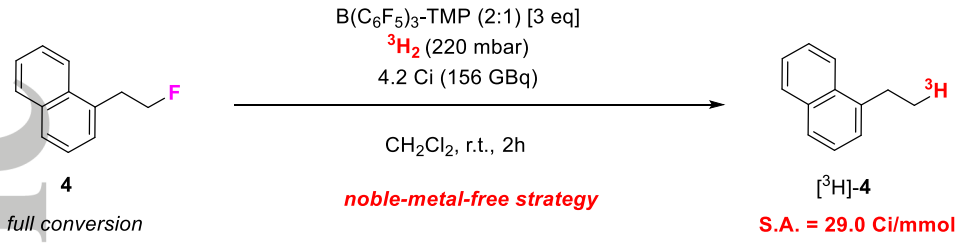
Figure 1: State-of-the-art approach used for hydrogendehalogenation labeling technique



Scheme 1: Proper substrates for successful C–F activation allowing ^{2}H-labeling by deuteride nucleophile attack; *i*) $^2H_2$ (1200 mbar); *ii)* 0.1M $B(C_6F_5)_3$, CH_2Cl_2; *iii)* TMP (neat), 1h, r.t.; *iv)* fluoroalkane, CH_2Cl_2; 16 h

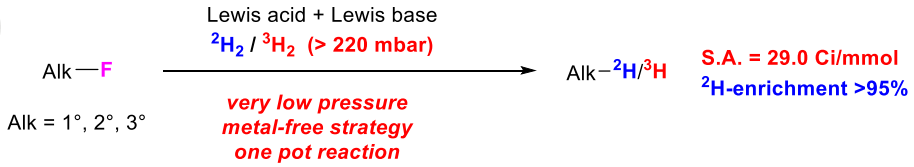


Scheme 2: Inert derivatives for C–F moiety activation; similar reaction conditions used as in Scheme 1



Scheme 3: Borane & FLP-assisted tritium labeling under very low pressure of tritium gas

Graphical Table of Contents



Reliable protocol for tritiodefluorination of alkylfluorides is reported. The described method is selective towards the F–C(sp^3) group and leaves both the aromatic F–C(sp^2) and F_2–C(sp^3) moieties unaffected. The site selectivity of the Lewis acid / [$TMP^{2(3)}H$][$^{2(3)}HB(C_6F_5)_3$] approach is orthogonal to currently used methods and allows for isotopic labeling of complementary positions in molecules.