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Pentafluorophenyl Esters: Highly Chemoselective Ketyl Precursors for the Synthesis of α,α-Dideuterio Alcohols Using SmI_2 and D_2O as a Deuterium Source

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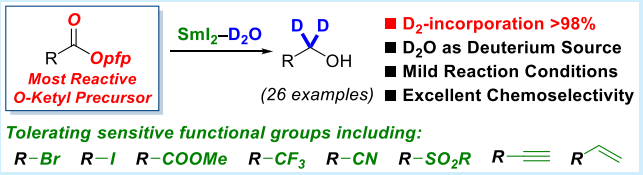
ABSTRACT: We report the first highly chemoselective synthesis of α,α-dideuterio alcohols with exquisite incorporation of deuterium (>98% [D_2]) using pentafluorophenyl esters as ketyl radical precursors, SmI_2 as a mild reducing agent, and D_2O as the deuterium source. This system tolerates a variety of functional groups, offering rapid entry to valuable α,α-dideuterated alcohol building blocks. More generally, this report introduces pentafluorophenyl esters as the most reactive *O*-ketyl precursors reported to date.



Deuterium-labeled compounds find wide applications in diverse fields of science,[1] including pharmaceutical development,[1a−d] materials science,[1e,f] analytical standardization techniques[1b] and toxicology studies.[1b] In principle, two general methods for deuterium incorporation have been developed: (1) small molecule synthesis[2] and (2) direct hydrogen-isotope-exchange.[3] The recent surge of interest in the synthesis of deuterated molecules has been bolstered by the U.S. Food and Drug Administration approval of the first [D]-containing drug, deutetrabenzine, which is a novel VMAT2 inhibitor for the treatment of cholera associated with Huntington's disease.[1d]

In this vein, we have described the synthesis of deuterated alcohols and amines using single-electron-transfer (SET) reagents.[2a−g] These methods offer the unique advantage of introducing deuterium by exploiting open-shell pathways via well-defined ketyl−metal complexes with high affinity for protic additives, which, in turn, enables the convenient use of D_2O or deuterated alcohols as the source of deuterium.

From the industrial standpoint, it is critical that high degrees of deuterium incorporation (>95% [D]) are achieved under mild, functional-group-tolerant, and user-friendly reaction conditions.[2] Typically, direct hydrogen-isotope-exchange methods do not allow for the exquisite degree of deuterium incorporation.[3a,b] Traditional reductive deuteration of esters mediated by expensive and pyrophoric $LiAlD_4$ affords α,α-dideuterio alcohols in high deuterium incorporations (Figure 1A).[2j] However, this strategy suffers from low functional group tolerance and limited scope. SET methods are more practical and routinely give high degrees of deuterium incorporation;[2a−g] however, these methods still fall short of the industrial standards.

In continuation of our studies, we recently questioned whether the use of activated esters might provide a mild route to deuterated molecules by the chemoselective generation of ketyl radicals.[4] Herein, we report the first highly chemoselective synthesis of α,α-dideuterio alcohols with an exquisite incorporation of deuterium (>98% [D_2]), using pentafluorophenyl esters as ketyl radical precursors and SmI_2 as a mild source of single electrons. There are two notable features of our findings:

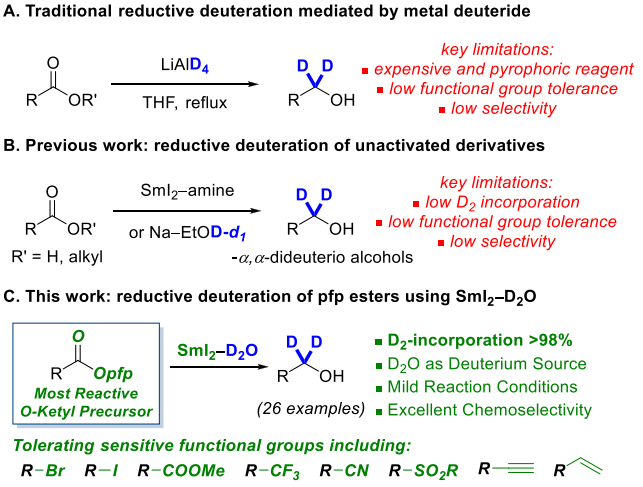


Figure 1. Reductive deuteration of esters: (a) traditional method, (b) previous studies, and (c) this work, using pentafluorophenyl (pfp) esters as the most reactive precursors to *O*-ketyl radicals.

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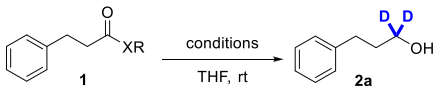
(1) the method represents the most efficient and functional-group tolerant synthesis of valuable α,α-dideuterated alcohol building blocks by a SET mechanism; and (2) more broadly, this report introduces pentafluorophenyl esters as the most reactive *O*-ketyl progenitors reported to date (see Figure 1). We anticipate that the synthesis of α,α-dideuterio alcohols and the capacity to selectively form ketyl radicals from readily available and bench-stable pentafluorophenyl esters will be of broad interest in various areas of SET reactions.[5,6]

Our studies commenced with the examination of various activated esters in the reduction using mild SmI_2–D_2O and SmI_2–MeOD-d_4 reagents (Table 1). We were delighted to find that the model pentafluorophenyl ester (pfp = C_6F_5) showed far superior reactivity to the analogous OPh, SEt, and OEt derivatives, while the SmI_2–D_2O system was more reactive than SmI_2–MeOD-d_4. Further optimization studies demonstrated that the yield of **2a** is influenced by the amount of both SmI_2 and D_2O, whereas it is noteworthy that high deuterium incorporation was uniformly obtained under different reaction conditions (see Table 2). When 6 equiv of SmI_2 was used, the amount of D_2O could be decreased from 200 equiv to 75 equiv without changes in yield (Table 2, entries 1–4). However, when the amount of D_2O decreased below 75 equiv, a steady decrease in the reaction yield was observed (Table 2, entries 5 and 6). The reductive deuteration of **1a** is a four-electron transfer process. The amount of SmI_2 could be decreased from 6 equiv to 5 equiv without detrimental effect on the yield (Table 2, entries 4 and 7). Shortening the reaction time from 15 min to 5 min or 30 s resulted in yields of 90% or 70%, respectively, which indicated that the half-life of this reaction is <30 s and the reaction required ~5 min to complete.

Table 1. Optimization Studies of the Leaving Group[a]

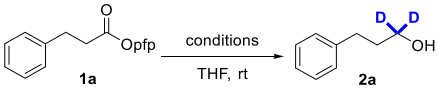


1 2a

entry	R	R′OD	R′OD (equiv)	SmI_2 (equiv)	yield[b] (%)
1	OPh	D_2O	200	6	20
2	OPh	CD_3OD	500	6	<5
3	SEt	D_2O	200	6	65
4	SEt	CD_3OD	500	6	10
5	OEt	D_2O	200	6	<5
6	OEt	CD_3OD	500	6	<5
7	Opfp	D_2O	200	6	>95
8	Opfp	CD_3OD	500	6	<5

[a]Conditions: **1** in tetrahydrofuran (THF) was added to a solution of SmI_2 in THF, followed by R'OD at room temperature (rt), and the resulting mixtures were stirred under Ar. [b]Determined by ^1H NMR.

Table 2. Optimization of the Reductive Deuteration of Pentafluorophenyl Esters, Using SmI_2–D_2O[a]



1a 2a

entry	SmI_2 (equiv)	D_2O (equiv)	time (min)	yield[b] (%)	$[D_2]$[b] (%)
1	6.0	200	15	>98	>98
2	6.0	150	15	>98	>98
3	6.0	100	15	>98	>98
4	6.0	75	15	>98	>98
5	6.0	50	15	85	>98
6	6.0	25	15	45	>98
7	5.0	75	15	>98	>98
8	4.0	75	15	75	>98
9	5.0	75	5.0	90	>98
10	5.0	75	0.50	70	>98

[a]Conditions: **1a** in THF was added to the solution of SmI_2 in THF, followed by D_2O at rt, and the resulting mixtures were stirred under Ar. [b]Determined by ^1H NMR.

Next, the scope of this transformation was investigated using the optimal conditions (Table 2, entry 7). As shown in Scheme 1, a remarkably broad range of aliphatic and aromatic pentafluorophenyl esters could be converted to the corresponding α,α-dideuterio alcohols in high yields and with excellent deuterium incorporation (Scheme 1). For the first time, >98% D_2 incorporation was obtained with each tested example by any SET process. Perhaps most notably, this method accommodates an array of functional groups that are sensitive to other electron transfer conditions, including chlorides (**2y** and **2o**), bromides (**2j**), iodides (**2k**), nitrile groups (**2l**), multiple fluorine substitutions (**2f** and **2i**), sulfonyl groups (**2m**), and alkynes (**2q**). Other functional groups such as methoxy (**2b**), thiomethyl (**2c**), phenolic hydroxyl (**2e**), sulfonamide (**2x**), and alkenes (**2w**) are also stable under the reaction conditions. Interestingly, conjugated alkenes, such as in perfluorophenyl (*E*)-3-(4-methoxyphenyl)acrylate (**1u**) can be fully reduced to give alcohols **2u** with exquisite deuterium incorporation in the sequential SET processes. Finally, it is important to note that a gram scale reaction (**2a**, see Scheme 1) also resulted in >98% D_2 incorporation. Of note, many of the products in Scheme 1 would not be accessible using metal deuterides or Na/EtOD-d_1.

To further demonstrate the synthetic utility of this reaction, we examined deuterations of pentafluorophenyl esters derived from pharmaceuticals (aspirin and probenecid) and fatty acids (oleic acid) (Scheme 1B). Pleasingly, >98% deuterium incorporation was obtained in each case (**2v**, **2w**, and **2x**), highlighting the potential of this protocol to introduce deuterium in medicinal chemistry and dietary supplements. We further demonstrated the synthesis of important deuterium-labeled building blocks (**2y** and **2z**) for the synthesis of deuterated drugs (Scheme 1C).[7]

Furthermore, as extremely useful building blocks, α,α-dideuterio alcohols can be converted to numerous deuterium labeled derivatives via well-established methods.[8] We have demonstrated that high deuterium incorporation content was well-preserved after oxidative (Dess–Martin oxidation),[8] basic (NaH deprotonation),[9] and acidic (Denton–Appel reaction)[10] reaction conditions (Scheme 1D), leading to useful deuterium-labeled aldehyde (**3**), ether (**4**), and halide (**5**) products with >98% D-incorporations.

Most remarkably, pentafluorophenyl esters can be selectively reduced in the presence of phenolic esters (**2v**) or alkyl esters (**2r** and **2s**), attesting to the outstanding chemoselectivity profile of the pfp group (see Schemes 1A and 1B). To further investigate the chemoselectivity of this reaction, we conducted competition experiments between pentafluorophenyl ester (**1d**) and representative carbonyl compounds (Scheme 1E). Remarkable selectivity versus carboxylic acid, ethyl ester, amide, and lactone substrates were observed, further highlighting the utility of pentafluorophenyl esters as the most reactive *O*-ketyl precursors discovered to date.

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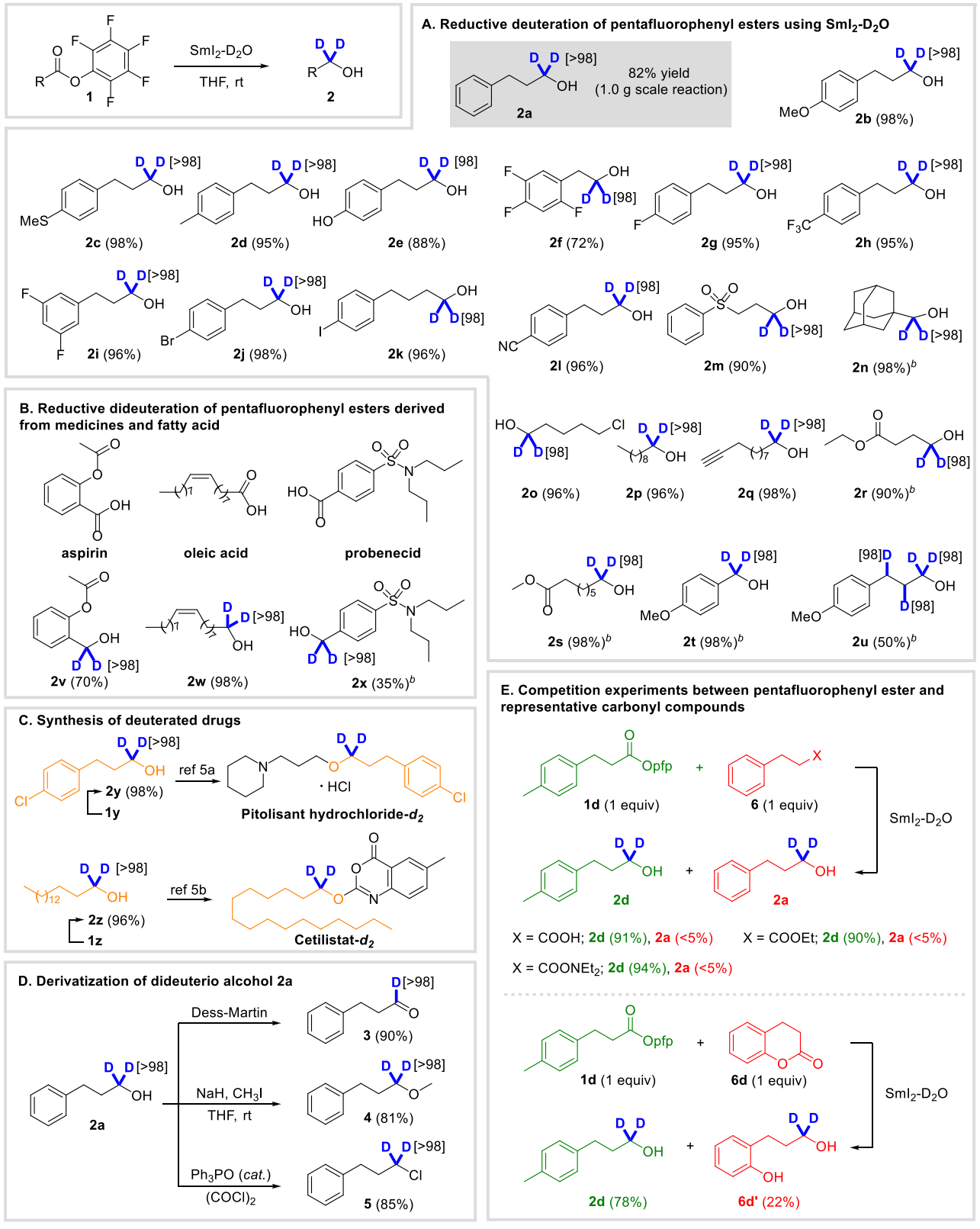
Scheme 1. Reductive Deuteration of Pentafluorophenyl Esters Using SmI_2–D_2O, Applications, Derivatization, and Competition Studies[a]



[a]Conditions: **1** (0.20 mmol, 1.0 equiv) in THF was added to the solution of SmI_2 in THF (5.0 equiv), followed by D_2O (75 equiv) at rt, and the resulting mixtures were stirred for 15 min under Ar. Isolated yields. [b]SmI_2 (7.0 equiv) and D_2O (105 equiv) were used.

Intrigued by the superb chemoselectivity of the reaction, we performed DFT calculations to probe the facility of ester reduction (B3LYP/6-311++G(d,p)) (Figure 2). The computational method reported by Nicewicz was employed to determine

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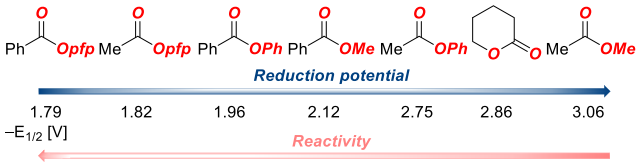

Figure 2. Redox potentials of *O*-ketyl precursors. Note that $MeCO_2pfp$ derived from *unactivated* alkyl precursor is characterized by a lower redox potential ($E_{1/2}$ = −1.82 V) than $PhCO_2Me$ derived from *activated* benzoic acid ($E_{1/2}$ = −2.12 V). See the Supporting Information (SI) for details.

electrochemical potentials.[11] To our delight, we found that the reduction potential of a model pfp acetate, $MeCO_2$-pfp, ($E_{1/2}$ = −1.82 V vs SCE in CH_3CN) is dramatically lower than that of methyl acetate, $MeCO_2$-Me ($E_{1/2}$ = −3.06 V vs SCE in CH_3CN) and phenyl acetate, $MeCO_2$-Ph ($E_{1/2}$ = −2.75 V vs SCE in CH_3CN), in agreement with the strong activating effect of the pfp group and the selectivity studies. Furthermore, the calculations suggest that the attachment of the pfp group to simple *unactivated* alkyl carboxylic acids has a comparable effect to using *activated* benzoic acids ($PhCO_2$-pfp, $E_{1/2}$ = −1.79 V vs SCE in CH_3CN; $PhCO_2$-Me, $E_{1/2}$ = −2.12 V vs SCE in CH_3CN; $PhCO_2$−Ph, $E_{1/2}$ = −1.96 V vs SCE in CH_3CN). This is much lower than that of a model six-membered lactone (tetrahydro-2*H*-pyran-2-one, $E_{1/2}$ = −2.86 V vs SCE in CH_3CN)—the most reactive *O*-ketyl precursor to date[2,4]—and in the range of simple ketones (PhCOMe, $E_{1/2}$ = −1.93 V vs SCE in CH_3CN).

In summary, the first highly chemoselective synthesis of α,α-dideuterio alcohols resulting in exquisite levels of deuterium incorporation (typically >98% [D_2]) has been developed under SET conditions using pentafluorophenyl esters as the most reactive *O*-ketyl precursors reported to date. A mild electron donor SmI_2 and a benign deuterium source D_2O were employed as reagents. This method is distinguished by its remarkable functional group tolerance, including even iodides, alkyl and phenolic esters, and lactones being tolerated. Furthermore, this protocol has been applied to the synthesis of key deuterated intermediates for the preparation of deuterated drugs. Derivatization studies demonstrated full preservation of the deuterium content under various conditions. The high reactivity of pentafluorophenyl ester as the *O*-ketyl precursor has been demonstrated experimentally and further established by determination of redox potentials. We anticipate that the high capacity of pentafluorophenyl esters to serve as *O*-ketyl precursors will be of interest in various areas of electron transfer. Further applications in SET reactions will be the subject of our future work.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04383.

Experimental details, characterization data, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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