Organic LETTERS

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Selective Synthesis of α,α-Dideuterio Alcohols by the Reduction of Carboxylic Acids Using SmI_2 and D_2O as Deuterium Source under SET Conditions

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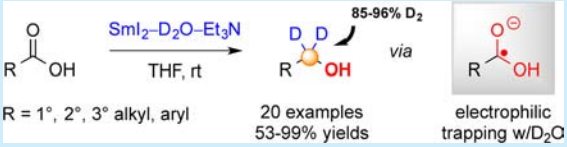
Supporting Information

ABSTRACT: The first general method for the chemoselective synthesis of α,α-dideuterio alcohols directly from feedstock carboxylic acids under single electron transfer conditions using SmI_2 is reported. This reaction proceeds after the activation of Sm(II) with a Lewis base, results in excellent levels of deuterium incorporation across a wide range of substrates, and represents an attractive alternative to processes mediated by pyrophoric alkali metal deuterides.



Recent studies demonstrate that the introduction of deuterium as a hydrogen bioisostere can have a major impact on improving pharmacokinetic properties (ADMET) of a large variety of drugs.[1] Most importantly, due to the primary deuterium kinetic isotope effect,[2] deuterium substitution at the metabolically labile sites can significantly increase stability of active pharmaceutical ingredients and reduce their toxicity by impeding formation of toxic metabolites (Figure 1).[3] As such, deuterium incorporation has experienced a renaissance of interest in the pharmaceutical industry,[1,4] and several deuterated drugs have been advanced to clinical trials.[1d] In addition, deuterated molecules are of high synthetic interest because of their use as tools for studying reaction mechanisms[5] and their application as functional materials[6] and as analytical standards in mass spectrometry.[7] Consequently, the development of new general protocols for the selective incorporation of deuterium is an important goal.

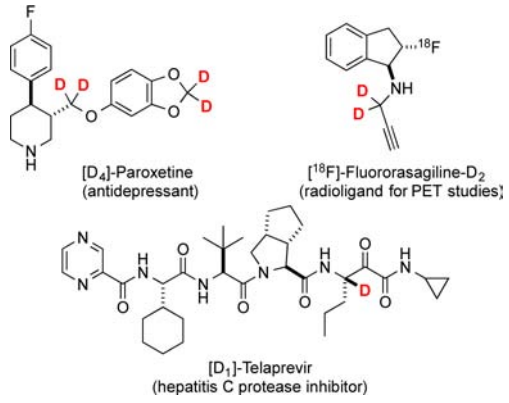


Figure 1. Recent examples of deuterated drug analogues. Deuterium used as a bioisostere of hydrogen to improve pharmacokinetic properties (ADMET = absorption, distribution, metabolism, excretion, toxicity).

Significant progress on the deuteration of organic molecules has been reported,[8] including pH-dependent[9a,b] and transition metal mediated[9c−f] protocols. However, the vast majority of these methods employ harsh reaction conditions, are limited in scope, or afford isotopically labeled products with moderate levels of deuterium incorporation.[8,9] Additional problems include nonselective labeling of several positions and lack of methods that would afford high selectivity in labeling of functional groups with similar reactivities. In addition, compared with deuteration of sp^2 or sp bonds (e.g. aromatic,[9a,c,g] vinylic,[9d] alkynyl[9b]), mild general methods for deuteration of unactivated sp^3 bonds are underdeveloped.[8,9e,f] There is no general deuteration method that involves a SET pathway.[10]

Since the pioneering studies by Kagan, SmI_2 has emerged as one of the most important single electron transfer reagents in organic synthesis.[11−13] Several methods employing SmI_2 to introduce deuterium to organic molecules have been reported.[14] In particular, Concellón and Rodríguez-Solla disclosed protocols for deuteration of activated π-bonds (Figure 2A);[14a−e] however, the potential of SmI_2 for the synthesis of isotopically labeled compounds has yet to be fully realized.[11]

We recently disclosed a practical method for the reduction of carboxylic acids via acyl-type radical intermediates using a reagent system prepared by activation of SmI_2 by Lewis base and water.[15] Crucially, the reaction was successfully applied to the reduction of a wide range of carboxylic acid feedstock materials bearing sensitive functional groups.[16]

To further expand this methodology, here we report the development of the synthesis of α,α-dideuterio alcohols by a

Received: August 13, 2014
Published: September 23, 2014

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dx.doi.org/10.1021/ol502404e | Org. Lett. 2014, 16, 5052−5055

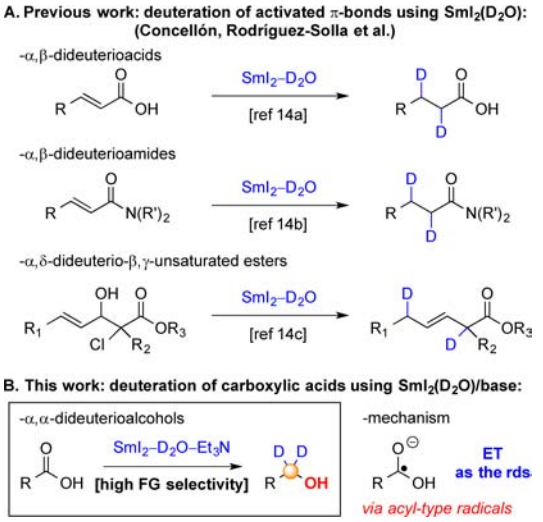


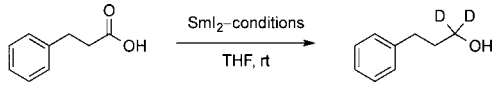
Figure 2. (a) Previous studies: dideuteration of activated π-bonds with SmI_2–D_2O. (b) This work: chemoselective synthesis of α,α-dideuterio alcohols via acyl-type radicals using SmI_2– D_2O–base.

direct reduction of carboxylic acids via radical intermediates using SmI_2 and D_2O as deuterium source (Figure 2B). There are several noteworthy features of this protocol: (i) very mild reaction conditions;[8] (ii) high functional group tolerance;[13] (iii) excellent levels of deuterium incorporation;[7] and (iv) the use of nonpyrophoric reagents in aqueous media.[17] In contrast to the synthesis of dideuterio alcohols using alkali metal deuterides, the current protocol can be readily applied to chemoselectively differentiate between functional groups with similar reactivities.[13] Furthermore, we demonstrate the preparation of deuterated compounds with a gradually increasing amount of deuterium label by exploiting a single electron transfer mechanism based on reversibility of electron transfer and formation of well-defined SmI_2–alcohol complexes with high affinity for Sm(II).[18] Finally, studies carried out during the development of the reaction suggest that in the Sm(II) reagents, amines can play a dual role as an intramolecular base and as a proton source, an observation that may have important implications for the future design and optimization of Sm(II) reagents.

We started our investigation by studying the effect of Lewis base and protic additives on D_2 incorporation in the reduction of 3-phenylpropanoic acid (Table 1). Because of its low price and ready availability,[19] D_2O was used as a preferred deuterium source. No reaction occurred in the absence of a proton source (entry 1). Pleasingly, the reaction in the presence of Et_3N as a Lewis base and D_2O as a proton source afforded the alcohol product in quantitative yield with 92.0% D_2 incorporation (entry 2). Premixing of acid with D_2O increases D_2 incorporation, presumably as a result of proton exchange (entries 2–4).[14a]

Deuterium incorporation depends on the reagent stoichiometry (entries 5–8). The best results were obtained in the presence of excess of D_2O (entry 8); however, all reaction conditions in which the additives were present in the required stoichiometry[18a] resulted in high levels of D_2 incorporation. The use of highly coordinating MeOD-d_4 was less effective (entry 9).[20] Primary and secondary amines promoted the reduction in excellent yields and in an instantaneous reaction time; however, much lower D_2 incorporation was observed (entries 10–15), consistent with the relative rates of the

Table 1. Effect of Additives on D_2 Incorporation in the Reduction of Unactivated Carboxylic Acids with SmI_2–D_2O[a]



entry	amine	ROH	equiv (R_3N)	equiv (ROH)	yield[b] (%)	$[D_2]$[b] (%)
1	Et_3N	D_2O	36		9.9	<2.0
2	Et_3N	D_2O	36	36	>98	92.0
3[c]	Et_3N	D_2O	36	36	>98	94.5
4[d]	Et_3N	D_2O	36	36	>98	93.5
5	Et_3N	D_2O	12	18	>98	84.5
6	Et_3N	D_2O	72	72	>98	94.0
7	Et_3N	D_2O	36	144	>98	92.5
8[e]	Et_3N	D_2O	36	288	>98	96.0
9	Et_3N	MeOD	36	36	21.5	34.0
10	n-$BuNH_2$	D_2O	36	36	>98	52.0
11	$C_5H_{10}NH$	D_2O	36	36	>98	27.5
12	C_4H_8NH	D_2O	36	36	>98	20.5
13	i-Pr_2NH	D_2O	36	36	>98	36.0
14[c]	i-Pr_2NH	D_2O	36	36	>98	67.5
15[d]	i-Pr_2NH	D_2O	36	36	>98	43.5

[a]Conditions: carboxylic acid (1 equiv), SmI_2 (6 equiv), THF, 23 °C. Addition order: acid, SmI_2, amine, D_2O. [b]Determined by ^1H NMR. [c]Addition order: acid, SmI_2, D_2O, amine. [d]Preformed solution of SmI_2/D_2O/amine. [e]Addition order: acid, D_2O, SmI_2, amine.

reduction.[18] Experiments conducted to investigate the potential for reagent complexation and proton exchange (entries 13–15) showed that proton transfer from amine occurs independently under the reaction conditions. Taken together, these experiments suggest that in reactions mediated by SmI_2–amine–water, amine can play a dual role as an intramolecular base and as a proton source before or after H^+ exchange, which is in contrast to previous studies suggesting that the major role of amine is to increase the redox potential of the reagent.[5a,15,18] The D_2 incorporation is consistent with the relative pK_{BH^+} of amines.[18d]

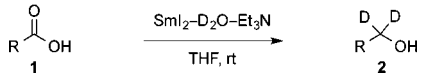
Scope studies showed that high levels of D_2 incorporation are general across a range of substrates, resulting in a broadly useful protocol (Table 2). Primary, secondary, tertiary, and aromatic ring-containing substrates afforded the dideuterated products with excellent D_2 incorporation (entries 1–4). Decarboxylation and aromatic reduction were not observed. Examination of a wide range of functional groups further demonstrates the broad scope of this protocol (entries 5–11). Importantly, several functional groups that are not compatible with other SET reagents were tolerated in the reaction (entries 5–8 and 11).

The sequential aryl bromide/acid reduction indicates the potential of this protocol for aryl-selective introduction of a deuterium label (entry 9).[21] Terminal olefins (entry 12) and heterocycles (entry 13) were tolerated. Moreover, protection of free N–H groups is not required to afford high levels of D_2 incorporation (entries 10 and 13). Finally, more complex substrates featuring activated benzylic and homobenzylic positions (entries 14 and 15) and unprotected alcohols, such as ursodeoxycholic acid (entry 16), readily participated in the reaction, maintaining excellent levels of D_2 incorporation.

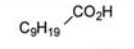
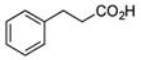
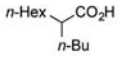
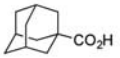
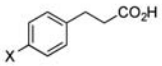
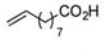
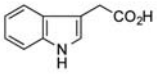
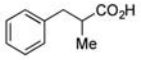
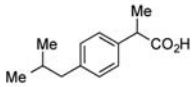
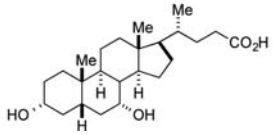
One of the advantages of using Sm(II) reagents to introduce deuterium lies in the ability to fine-tune the redox potential (E° = 0.9 to 2.8 V) to a specific moiety.[11−13] This can result in high

dx.doi.org/10.1021/ol502404e | Org. Lett. 2014, 16, 5052–5055

Table 2. Effect of Structure on D_2 Incorporation in the Reduction of Carboxylic Acids with SmI_2–D_2O[a]



1 2

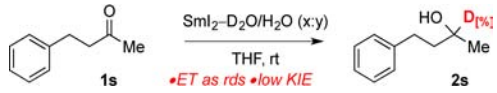
entry	1	carboxylic acid	yield of 2 (%)	$[D_2]$[b] (%)
1	1a		95	93.0
2	1b		94	91.5
3	1c		91	94.0
4	1d		88	92.0
				
5	1e	X = MeO	91	91.0
6[c]	1f	X = CF_3	81	92.5
7	1g	X = F	94	92.0
8[d]	1h	X = Cl	74	92.5
9[e]	1i	X = Br	79	93.5
10	1j	X = 4-NH_2	53	88.5
11	1k	X = 4-MeS	93	92.5
12	1l		92	91.5
13	1m		61	85.5
14	1n		99	91.5
15	1o		98	93.5
16	1p		86	88.0

[a]Conditions: carboxylic acid, SmI_2 (6 equiv), THF, D_2O (36 equiv), Et_3N (36 equiv), 23 °C. [b]Determined by ^1H NMR. [c]96:4 ratio of **2f** to 1,1-*D*,*D*-3-(*p*-tolyl)propan-1-ol. [d]88:12 ratio of **2h** to 1,1-*D*,*D*-3-phenylpropan-1-ol. [e]>95% conversion to 1,1-*D*,*D*-3-(4-deuteriophenyl)propan-1-ol; 76% $[D_1]$ at the aromatic ring.

chemoselectivity simply by changing the required additive. The developed SmI_2–D_2O conditions can be applied to the synthesis of α-mono and α,α-dideuterio alcohols from a variety of functions, such as aldehydes (**1q**), chlorides (**1r**), ketones (**1s**), esters (**1t**), and amides (**1u**) (Table 1-SI, Supporting Information).

Furthermore, the present reaction can be readily applied to the targeted titration of deuterium content to afford products with increasing amount of deuterium simply by using a combination of H_2O and D_2O (Table 3 and Figure 3: correlation curve, R^2 = 0.99).[8,9] Note that this outcome is possible on the basis of rate-limiting electron transfer,[18] low kinetic isotope effect to carbon,[5,15,18] and the use of user-friendly aqueous conditions in the reaction.[17] A similar titration would be difficult to achieve using pyrophoric metal deuterides.

Table 3. Application of SmI_2–D_2O/H_2O to Targeted Incorporation of Deuterium Content[a]



1s 2s

entry	D_2O/H_2O (x:y, %)		conv (%)	yield of **2s** (%)	$[H_1/D_1]$ (%)
1	100	0	>98	96	<2
2	80	20	>98	94	31.5
3	60	40	>98	93	54.5
4	40	60	>98	92	70.5
5	20	80	>98	94	85.5
6	0	100	>98	93	>98

[a]Conditions: substrate, SmI_2, THF, D_2O/H_2O (200 equiv), 23 °C.

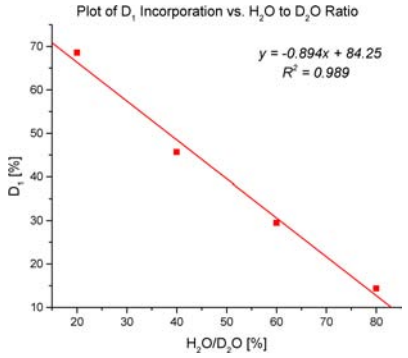
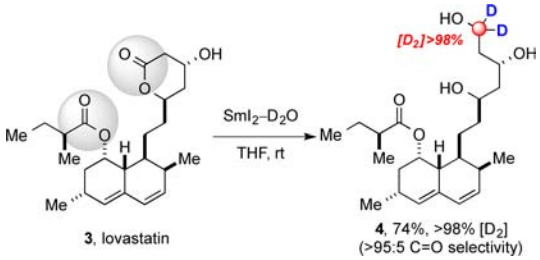


Figure 3. Calibration curve for targeted incorporation of deuterium using SmI_2–D_2O/H_2O in the reduction of **1s**.

To further demonstrate the synthetic utility of the reaction, we examined deuteration of lovastatin,[16d] a cholesterol-lowering drug, featuring a six-membered lactone and acyclic ester in a sensitive decalin ring (Scheme 1). The dideuterated

Scheme 1. Chemoselective Dideuteration of Lovastatin



product resulting from lactone reduction was obtained with complete selectivity (>98% D_2),[13] demonstrating the potential of this protocol to chemoselectively introduce D_2 in complex settings.

In conclusion, α,α-Dideuterio alcohols can be synthesized directly from carboxylic acid feedstocks using SmI_2 and D_2O as deuterium source. The reaction conditions are mild and result in high levels of deuterium incorporation to give alcohol products via a general single electron transfer mechanism. The protocol can also be extended to other functional groups, targeted titration of deuterium, and deuteration of complex molecules. Amines can serve as an intramolecular proton source, which could lead to the discovery of novel two-component Sm(II) reagents and the development of catalytic Sm(II) protocols.

dx.doi.org/10.1021/ol502404e | Org. Lett. 2014, 16, 5052–5055

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the EPSRC and Leverhulme Trust for support. M.S. thanks Rutgers University for support during the preparation of this manuscript.

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