Organic LETTERS
Letter
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

Transition-Metal-Free, Selective Reductive Deuteration of Terminal Alkynes with Sodium Dispersions and EtOD-d_1

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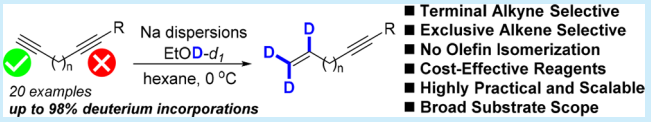
Supporting Information

ABSTRACT: A transition-metal-free single electron transfer reaction has been developed for the synthesis of [D_3]-alkenes from terminal alkynes using sodium dispersions as the electron donor and EtOD-d_1 as the deuterium source. Both reagents are cost-effective and bench-stable. This practical method exhibits remarkable terminal alkyne selectivity and exclusive alkene selectivity. Excellent deuterium incorporations and yields were achieved across a broad range of terminal alkynes without olefin isomerization. Of note, this reaction is highly solvent dependent. *n*-Hexane provides unique enhancement to this reductive deuteration process.



Selective deuterium substitution of physiologically active compounds can result in longer half-lives and improve safety due to higher stability of C−D bonds than C−H bonds.[1] With the recent renaissance of deuterated drugs, a considerable amount of deuterium-containing agents have entered clinical trials (Figure 1a).[1] In 2017, the US Food and Drug Administration (FDA) awarded a new chemical entity to the first deuterated drug, deutetrabenazine, which is recognized as a different orphan drug for the treatment of chorea versus tetrabenazine (Figure 1b). In addition, deuterium labeled compounds have been widely used as metabolic or pharmacokinetic probes,[2] internal standards in analytical chemistry,[3] and tools for elucidation of reaction mechanisms[4] (Figure 1c).

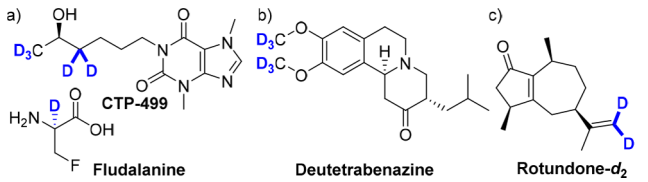
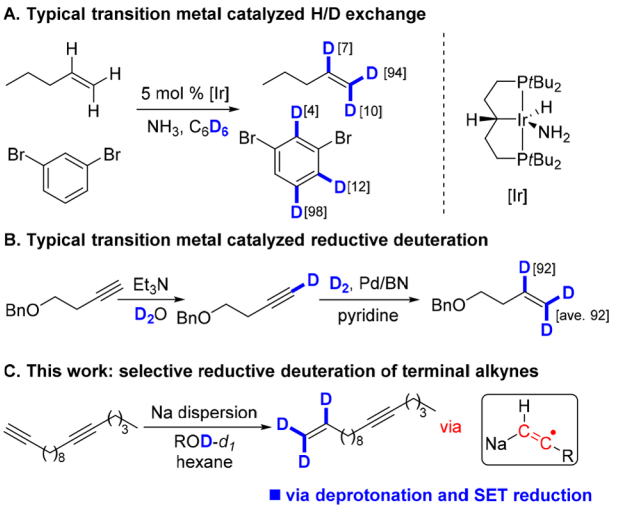


Figure 1. (a) Selected examples of deuterated drugs advanced to clinical trials, (b) deutetrabenazine, and (c) deuterium-labeled internal standard.[3b]

Terminal alkenes are useful building blocks as well as valuable end products, present in a plethora of pharmaceuticals, agrochemicals, and natural products. H/D exchange and reductive deuteration are two strategies generally employed for the selective introduction of deuterium into the vinyl groups. Transition metal catalyzed postsynthetic H/D exchange[5] is a universal strategy, albeit it often requires harsh reaction conditions and suffers from poor regioselectivity and low deuterium incorporations (Scheme 1A). As alkenes are typically synthesized by semihydrogenation of the corresponding alkynes,[6] reductive deuteration represents a more straightforward strategy.[7] In fact, transition-metal-catalyzed semireduction of terminal alkynes in the presence of D_2 gas,[7b,d,e] organosilanes/D_2O,[7a] or CO/D_2O[7c] have resulted in better regioselectivity and higher deuterium incorporations than H/D exchange (Scheme 1B). However, if [D_3]-alkene is the designed product, [D_1]-alkynes have to be used as the corresponding starting materials (Scheme 1B).[7b] Unfortunately, over-reduction associated with the reduction process makes this strategy less synthetically attractive. In addition, expensive transition-metal catalysts, reductants, and deuterium sources employed in both of these strategies (Scheme 1A,B) have thus far restricted industrial applications.

Previously, we have demonstrated the alkali-metal-mediated single electron transfer (SET) as an emerging strategy for the reductive deuteration of carboxylic esters and activated alkenes.[9] Herein, we report the first selective SET reductive deuteration of

Scheme 1. Strategies for the Synthesis of [D_3]-Alkenes[8]



Received: April 2, 2018

DOI: 10.1021/acs.orglett.8b01036
Org. Lett. XXXX, XXX, XXX−XXX

alkynes mediated by sodium dispersions and the readily available ROD-d_1. Both reagents, i.e., the electron and deuterium donor, are bench-stable and commercially available. This strategy is amenable to scale-up, and the application of Na dispersions in industry synthesis has already been demonstrated.

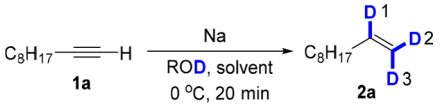
Traditionally, alkyne reduction can be achieved by dissolved alkali metal in either liquid ammonia or HMPA (Birch conditions).[10] As the soluble electride derived from Na and liquid NH_3 is a very powerful reductant, both internal and terminal alkynes and even aromatic or heteroaromatic moieties are reduced via an outer sphere electron transfer process. Additionally, toxic ammonia, tedious experimental procedures, and the problems associated with over-reduction and olefin isomerization have made this classical method less attractive. Furthermore, direct reduction of alkynes by a sodium lump is impractical, as this heterogeneous reaction is extremely slow.

In this study, we report that commercially available sodium dispersions (particle size 5−10 μm) with high specific surface area significantly increase the rate of alkyne reduction and, remarkably, reduce terminal alkynes with high selectivity via an inner sphere electron transfer process (Scheme 1C). We show that in the presence of a deuterium donor unlabeled terminal alkynes can be directly converted into [D_3]-alkenes in a single step by sodium dispersions. This reaction involves two processes: (i) reductive deuteration of the triple bond and (ii) the H/D exchange of the terminal hydrogen. We found that subjecting a terminal alkene, dec-1-ene, to Na/EtOD-d_1 led to no detectable H/D exchange, which indicates that H/D exchange happened before the reduction via the formation of an acetylide anion. Our method shows the following advantages compared with other reductive deuterations of alkynes: (a) excellent terminal alkyne selectivity, (b) using all hydrogen alkyne as the starting material to synthesized [D_3]-alkene in a single step, and (c) much cheaper and more convenient to use reagents and reaction conditions.

On the basis of this observation, the reaction conditions were optimized using an unactivated terminal alkyne **1a** (Table 1). Excellent yield and deuterium incorporation were obtained using 10 equiv of sodium dispersion/deuterium donor in hexane at 0 °C (entry 4). Significantly, the side reaction between deuterium donors and sodium to generate deuterium gas was relatively slow, compared to the electron transfer process. In addition, the use of sodium dispersions obviates the hazards associated with traditional alkali metal-mediated reactions. Traditional sodium-mediated reactions, for example, Bouveault−Blanc reduction, normally require reflux conditions and may result in excessive foaming and even fire. This reaction was found to be highly solvent dependent (entries 4−7). In *n*-hexane, sodium dispersion exhibits uniquely enhanced reductive ability toward terminal alkynes, whereas in THF, Et_2O, or toluene, the yields dropped dramatically from >98% to <5% (entries 5−7). We hypothesize that solvents with higher dielectric constant, such as THF, would facilitate an outer sphere electron transfer process,[11] while solvents with low dielectric constants, such as hexanes, should favor the inner-sphere mechanism. As expected, a sodium lump led to much lower conversion (entry 8). Finally, variations in the addition order resulted in lower deuterium incorporation (entry 9).

Next, the optimized conditions were applied to the selective reductive deuteration of different classes of alkynes (Tables 2). A broad range of terminal alkynes were converted to the corresponding [D_3]-alkenes with excellent deuterium incorporation and in high yields. Remarkably, unactivated internal alkynes and aromatic groups were found to be very stable under

Table 1. Optimization Studies in the Reductive Deuteration of Alkynes[a]

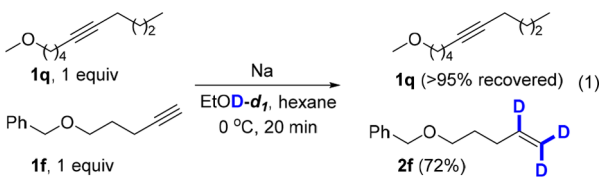


entry	Na (equiv)	ROH (equiv)	solvent	yield[b] (%)	[D][b] at positions 1, 2, and 3 (%)
1	4.0	EtOD-d_1 (4.0)	hexane	77	63, 48, 72
2	6.0	EtOD-d_1 (6.0)	hexane	79	74, 50, 82
3	8.0	EtOD-d_1 (8.0)	hexane	84	91, 71, 88
4	**10.0**	**EtOD-d_1 (10.0)**	**hexane**	**98**	**96, 82, 96**
5	10.0	EtOD-d_1 (10.0)	THF	<5	
6	10.0	EtOD-d_1 (10.0)	Et_2O	<5	
7	10.0	EtOD-d_1 (10.0)	toluene	<5	
8[c]	10.0	EtOD-d_1 (10.0)	hexane	19	
9[d]	10.0	EtOD-d_1 (10.0)	hexane	98	72,70,82

[a]Conditions: sodium dispersions in oil (29 wt %, particle size 5−10 μm) was added to a solution of **1a** (0.50 mmol, 1.0 equiv) and EtOD-d_1 at 0 °C, and stirred for 20 min under N_2. [b]Determined by ^{1}H NMR. [c]Sodium lump. [d]EtOD-d_1 was added 20 min after the addition of sodium.

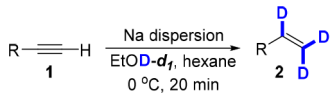
the developed conditions, which is in contrast to the classic Birch-reduction.

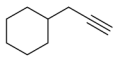
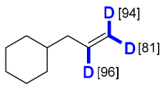
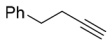
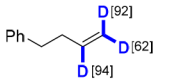
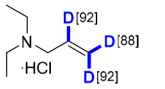
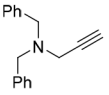
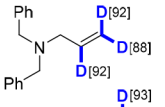
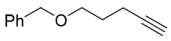
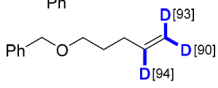
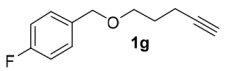
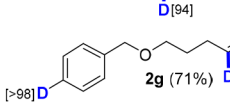
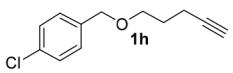
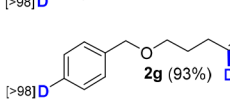
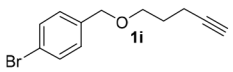
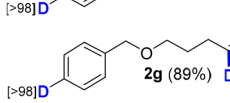
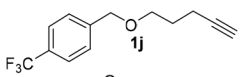
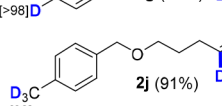
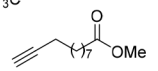
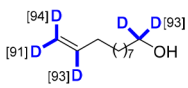
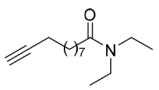
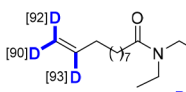
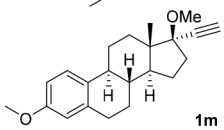
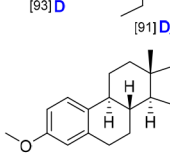
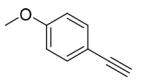
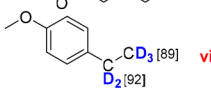
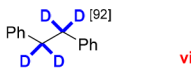
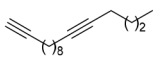
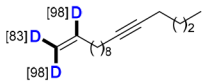
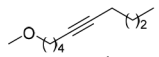
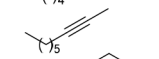
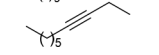
This method is compatible with a broad range of functional groups, including aromatic rings (**1c**, **1g**−**1j**), tertiary amines (**1d**, **1e**), ethers (**1f**−**1j**, **1m**−**1n**), and amides (**1l**). The removal of benzylic protecting groups from alcohols (**1f**) and amines (**1e**) was not detected. Terminal alkynes with increasing steric demand at the α-carbon were suitable substrates for the reduction (**1b**, **1m**). Over-reduction and olefin isomerization were not observed, except for stabilized benzyl radicals, which is a significant advantage compared to the traditional Na/NH_3 system. As an exception, phenyl-substituted alkyne **1n** was fully reduced to alkane. Halides (**1g**−**1j**) were reduced with >90% deuterium incorporations without the use of additional reagents, which suggests a potential in the selective halogen-deuterium exchange. The ester group (**1k**) was sequentially converted to the α,α-dideuterio alcohol with high deuterium incorporation. It is noteworthy that scaling up this reaction (from 0.50 to 10 mmol) had little influence on the yield and deuterium incorporation (**1c**, Table 2). Unactivated internal alkynes (**1q**, **1r**, **1s**) are very stable under the reaction conditions. Note that, while 1,2-diphenylethyne (**1o**) can undergo reduction, this process likely involves an aryl radical pathway. Finally, full selectivity in the reduction of terminal alkynes in the presence of internal alkynes was achieved in both intermolecular (eq 1) and intramolecular (**1p**, Table 2) competition reactions.



DOI: 10.1021/acs.orglett.8b01036
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Reductive Deuteration of Terminal Alkynes by Na/EtOD-d_1[a]

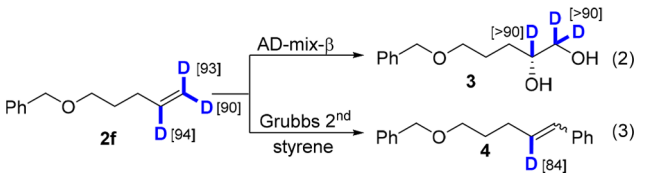


substrate		product	
	1b		2b (83%)
	1c		2c (86%) (85%)[b]
	1d		2d (67%)
	1e		2e (97%)
	1f		2f (83%)
	1g		2g (71%)
	1h		2g (93%)
	1i		2g (89%)
	1j		2j (91%)
	1k		2k (86%)
	1l		2l (81%)
	1m		2m (98%)
	1n		2n (93%) via aryl radical
	1o		2o (74%) via aryl radical
	1p		2p (95%)
	1q	only starting material recovered	
	1r	only starting material recovered	
	1s	only starting material recovered	

[a]Isolated yields. Percentage of exchanged protons at the specified position are indicated in brackets, determined by ^{1}H NMR. [b]10.0 mmol scale.

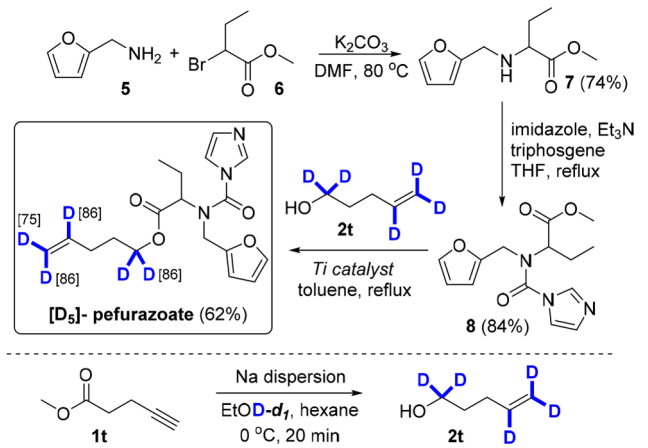
High terminal selectivity may result from two possible scenarios: (a) steric hindrance of the internal alkyne and (b) deprotonation/activation pathway. An acetylide anion derived from deprotonated terminal alkyne may easily be adsorbed onto the surface of the positively charged sodium particles. Under heterogeneous conditions, electron transfer only occurs on the surface of the sodium particle. Thus, the ET process may be accelerated after deprotonation. However, it is noteworthy that this reaction is significantly slower than most other sodium-mediated SET reactions, such as Birch reduction or Bouveault–Blanc reduction. Monitoring of the present reaction demonstrated a $t_{1/2}$ of about 10 min. Decreasing the reaction time to 3 min led to significantly lower conversions. The kinetic isotope effect determined using **1c** (k_H/k_D = 1.2 ± 0.1) demonstrated that deuterium transfer is unlikely to be the rate determining step of this reaction.[12] Moreover, cleavage of the methoxy group in **1m** revealed that the radical anion intermediate derived from the first electron transfer (Scheme 1C) is relatively stable, suggesting that the second electron transfer might be the slow step of this reaction.

As extremely useful building blocks, terminal [D_3]-alkenes can be used for the construction of complex deuterium-containing labels via well-established methods including cross-metathesis, epoxidation, ozonolysis, cyclopropanation, Sharpless dihydroxylation, and Wacker oxidation. Taking **2f** as an example, we demonstrated that high deuterium incorporation content is well-preserved after derivatization by Sharpless dihydroxylation (eq 2) or olefin metathesis (eq 3).



To further explore the synthetic utility of this new deuteration method, [D_5]-pefurazoate was synthesized using the route illustrated in Scheme 2. Pefurazoate is a marketed imidazole-containing fungicide used for seed treatment. As shown, high, site-specific deuterium incorporation was achieved in the final product, which constitutes an attractive target for isotope dilution analysis. The antifungal activity of [D_5]-pefurazoate will be evaluated and compared with the all hydrogen analogues in our further studies.

Scheme 2. Synthesis of [D_5]-Pefurazoate[9]



In summary, we have developed a practical reductive deuteration method of terminal alkynes mediated by sodium

DOI: 10.1021/acs.orglett.8b01036
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dispersion as the electron donor and EtOD-d_1 as the deuterium donor. This method is operationally trivial and scalable and represents the first reductive deuteration method that converts unlabeled alkynes into [D_3]-alkenes in a single step. This method displays remarkable selectivity toward terminal alkyne groups in that over-reduction of the alkyne and olefin isomerization are not observed. The utility has been demonstrated in the synthesis of a broad range of [D_3]-alkenes with high deuterium incorporation and in high yields. The labeled [D_3]-alkenes have been derivatized with full preservation of the deuterium content. The successful synthesis of [D_5]-pefurazoate demonstrates the potential application of this method in the synthesis of new deuterium-labeled bioactive compounds. Compared with the current transition-metal-catalyzed reductive deuteration methods and H/D exchange reactions, this developed method is more efficient and sustainable and operates with lower cost and higher atom-economy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01036.

General experimental procedures, characterization of new compounds, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Key Research and Development Plan of China (2017YFD0200504) and the National Natural Science Foundation of China (No. 21602248, 21711530213) for financial support.

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