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Practical Method for Reductive Deuteration of Ketones with Magnesium and D_2O

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Cite This: https://dx.doi.org/10.1021/acs.orglett.9b04536 Read Online

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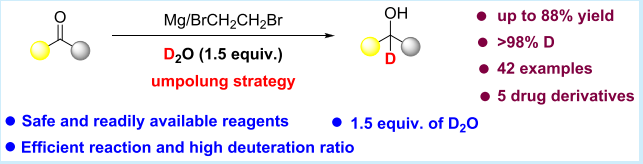
ABSTRACT: α-Deuterated alcohols have important applications in pharmaceuticals and mechanism studies. Here, we report a new and practical strategy for the reductive deuteration of ketones using a $Mg/BrCH_2CH_2Br/D_2O$ system, which affords α-deuterated alcohols in good yields and with almost quantitative incorporation of deuterium. The synthetic value of this method has been demonstrated by the easy access to deuterated drugs or drug derivatives. This method may inspire the discovery of other deuterium-containing drugs.



Since deuterium was discovered in 1931 by Harold C. Urey,[1] who received the 1934 Nobel Prize for his contributions, there has been significant interest in the use of deuterium, and the number of deuterium-labeled compounds reported has increased dramatically.[2] Examples of the use of deuterium to facilitate mechanistic, spectroscopic, and tracer studies can be found within almost every subdiscipline in the life and physical sciences.[3] Among these applications, preparation of deuterated pharmaceuticals and other biologically active compounds attracted great attention because the precision deuteration of drugs allows one to proceed beyond establishment of the pharmacokinetic parameters of a drug and might provide an opportunity to solve problems of metabolism-mediated toxicity, drug interactions, and low bioactivation.[4] The use of deuterium also offers opportunities to discover new drugs by merely substituting deuterium for hydrogen in drugs that have already been approved.[5] α-Deuterated alcohols[6] enjoy a range of uses. They work as key intermediates in the processing of deuterium-containing biologically active compounds, including deuterium-containing drugs (Figure 1A).[7] They serve as deuterium sources in the synthesis of other deuterated compounds and have potential applications in material science.[8] Reductive deuteration of carbonyl compounds is the most straightforward process to deliver α-deuterated alcohols.[6a−c] In principle, there are several different strategies based on different mechanistic pathways to reduce carbonyl compounds to α-deuterated alcohols (Figure 1B). Nucleophilic addition of a deuteride anion (D^-) to a carbonyl group (Strategy A) is the traditional pathway. Alkali metal deuteride salts like lithium aluminum deuteride ($LiAlD_4$) or sodium borodeuteride ($NaBD_4$) serve as the common sources of the deuteride anion.[2j] The deuteride species can also be generated *in situ* from metal catalysts and D_2 in the form of deuterium gas or its precursors.[9] Meerwein−Ponndorf−Verley reduction, a frequently used method for the reductive hydrogenation of carbonyl compounds, features rearrangement between carbonyl compounds and secondary alcohols (Strategy B) and could be adopted to deuterated version if α-deuterated secondary alcohols are applied.[10] Single electron reduction (SER) by a reducing reagent to form a carbon radical which abstracts a deuterium from the surrounding molecules is another potential pathway but would be less useful as this method not only suffers from the tendency of the carbon radical to dimerize, producing pinacol-type products, but also needs expensive R-D reagents like d_8-THF (Strategy C). The umpolung strategies D[11] undergo double SER to directly afford carbanion species that can be deuterated to produce α-deuterated alcohols. In terms of a practical and general synthesis of α-deuterated alcohols in large quantities, the umpolung strategies which use D_2O as the deuterium source have great advantages in price, supply, and safety. Among all these deuterium sources utilized in strategies A−D, D_2O is the best reagent because it can be obtained in large quantities at the lowest price.[12] For general comparison, the price of D_2O is only 2% of that for $NaBD_4$ and 0.2% of that for $LiAlD_4$. However, the umpolung strategies have rarely been utilized in the reductive deuteration of ketones because these methods would require a large excess amount of D_2O or CD_3OD (typically more than 100 equiv).[13]

Herein, we report a practical method for the reductive deuteration of ketones with a $Mg/BrCH_2CH_2Br/D_2O$ system, affording α-deuterated alcohols in yields as high as 88% and deuterium incorporation in excess of 98%. Only 1.5 equiv of D_2O is required for the deuteration, while alternative methods need a large excess amount of D_2O or CD_3OD.

Received: December 18, 2019

https://dx.doi.org/10.1021/acs.orglett.9b04536
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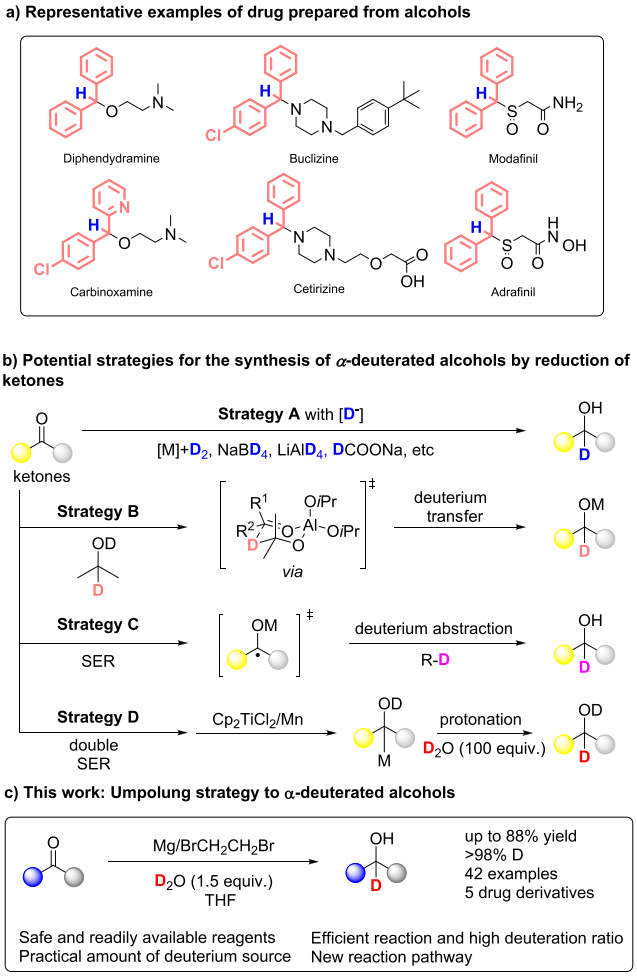

Figure 1. (a) Representative examples of drugs prepared from alcohols. (b) Potential strategies for synthesis of α-deuterated alcohols by the reduction of ketones. (c) This work.

As shown in Figure 2, we began our study by screening the additives required for the reaction of benzophenone (**1**) in THF with a stoichiometric amount of D_2O as the deuterium source. The desired reductive deuteration product (**1a**) together with the accompanied pinacol (**1b**) were formed, but control of the selectivity was challenging. With LiCl or MgI_2 as the additive, the reaction failed to deliver either the targeted deuterated alcohol (**1a**) or the pinacol **1b** (Figure 2). When dibromomethane was employed as the additive, the reaction afforded the α-deuterated alcohol (**1a**) in 7% yield although with only 40% deuterium incorporation. 1,2-Dibromoethane promoted the reaction, giving the α-deuterated alcohol (**1a**) in 83% yield with more than 98% deuterium incorporation and only 12% of pinacol (**1b**) as the byproduct. Other alkyl bromides were investigated but failed to further improve either the yield or the deuterium incorporation. 1,2-Dibromoethane appears to assume a unique role in this reaction. Control experiments without the addition of magnesium or $BrCH_2CH_2Br$ were also carried out, and only a trace amount of the desired products was detected in both cases. The use of only 1.5 equiv of D_2O demonstrates that this method is highly efficient, economical, simple, and useful for the synthesis of deuterated alcohols from carbonyl compounds.

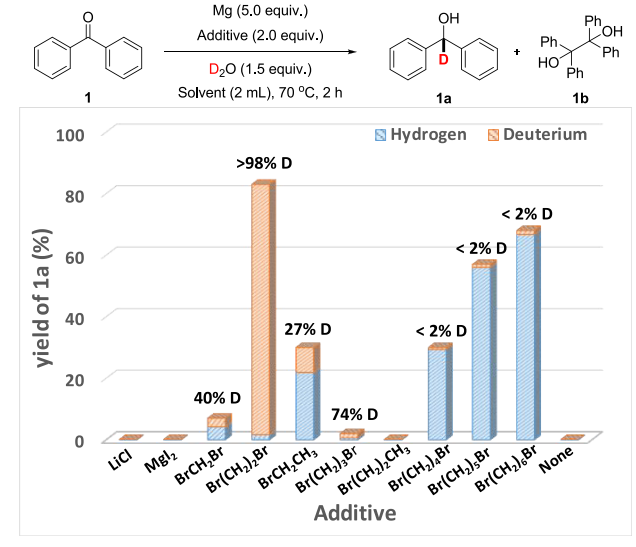

Figure 2. Reductive deuteration of ketones with different additives.

With the optimal reaction conditions in hand, the scope of substituted benzophenones was investigated, and the results are summarized in Figure 3. In general, the variously substituted benzophenones can be transformed into the desired products in good yields and with >96% deuterium incorporation. Substrates with a moderate electron-withdrawing group, such as fluorine or chlorine, afforded the corresponding products (**2a**−**10a**) in moderate to good yields. Strong electron-withdrawing groups, such as the cyano (**11**) and ester groups (**12**), which are sensitive under conditions of the Grignard reaction, are also tolerated. Moreover, a terminal olefin (**13**) that tends to be reduced with magnesium/methanol remained unaffected under the reaction conditions.[14] The reactions occurred smoothly with substrates containing an electron-donating group, such as Me, ^{t}Bu, OMe, Ph, and NMe_2, and delivered the corresponding product in 48−86% yields (**14a**−**31a**).

We explored the scope of other type of ketones. Substrates with a five-, six-, or seven-membered ring underwent the reaction smoothly to produce the corresponding products (**32a**−**35a**) in 57−88% yields and with up to 97% deuteration incorporation. The reactions also proceeded well with pyridines, affording the target products in 61−82% yields (**38a**−**41a**). A pyridine-fused tricyclic compound participated in the reaction and afforded the desired product (**42a**) in 88% yield. The two symmetric diketones that were tested offered an opportunity for the selective reduction of one of the carbonyl groups and afforded the monodeuterated products (**43a** and **44a**) in moderate yields with the second carbonyl group untouched. As examples, monoaryl ketone (**36**) and dialkyl ketone (**37**) did not work well under the optimal reaction conditions.

To explore the synthetic potential of this method, direct reductive deuteration of the drug molecules and synthesis of various deuterated drug molecules was carried out as shown in Figure 4. Fenofibrate,[15] a drug for the treatment of hyperlipidemia, mixed dyslipidemia, and hypertriglyceridemia, can be selectively reduced to the corresponding deuterated alcohols (**45a**). Esters, chlorides, and ethers are tolerated well under the reductive conditions. Furthermore, several other types of deuterated drugs or drug precursors were synthesized through the current reductive deuteration method. First, we examined the deuteration of diphenhydramine,[16] a histamine antagonist with antiallergic activity. Under basic reaction

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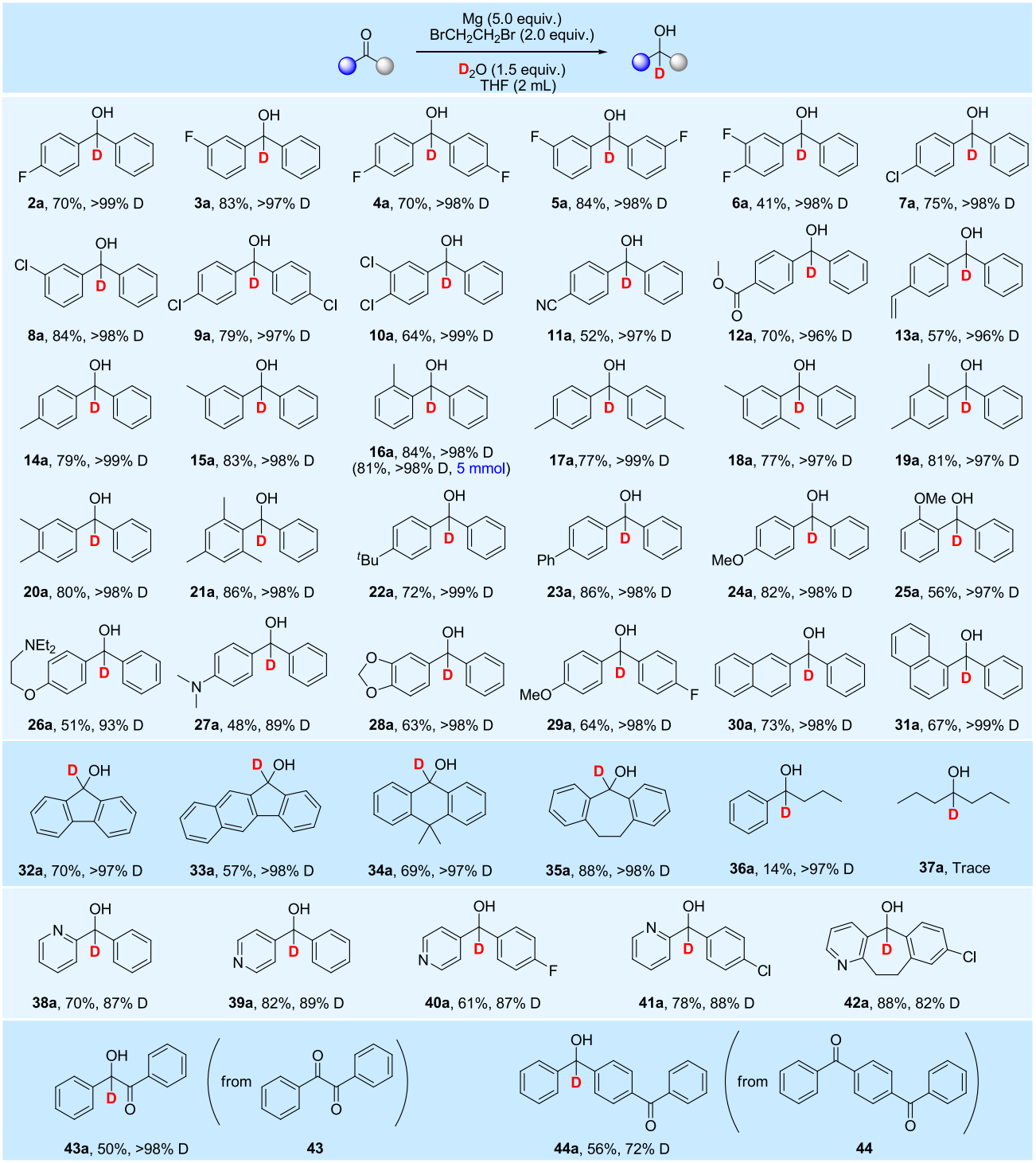

Figure 3. Substrate scope. Reaction conditions: ketone (1.0 mmol), $BrCH_2CH_2Br$ (2.0 equiv), Mg (freshly peeled, 5.0 equiv), and D_2O (1.5 equiv) in THF (2 mL) at 70 °C for 2 h unless otherwise noted in the Supporting Information; isolated yield.

conditions, nucleophilic attack on chloroamine (**52**) by α-deuterated alcohol (**1a**) led to the formation of deuterated diphenhydramine (**46a**) in an excellent yield and with almost quantitative deuterium incorporation. Buclizine[7a,17] is an antagonist with primarily antiemetic and antivertigo activities. One-pot treatment of α-deuterated alcohol (**7a**) with substituted piperazine (**53**) gave deuterated buclizine (**48a**) in a moderate yield and without any deuterium loss. The deuterated chloride intermediate (**47a**) that is important in the synthesis of buclizine might also be used for other valuable structural modifications. In addition, modafinil and adrafinil,[18] central nervous system stimulants, have a sensitive sulfinyl group and an amide. Nucleophilic attack of 2-mercaptoacetic acid with an α-deuterated alcohol (**1a**) would afford deuterated (benzhydrylsulfanyl)acetic acid (**49a**), which can be used as the precursor for the synthesis of deuterated modafinil (**50a**) and deuterated adrafinil (**51a**) according published methods.[18b] In general, we developed an efficient

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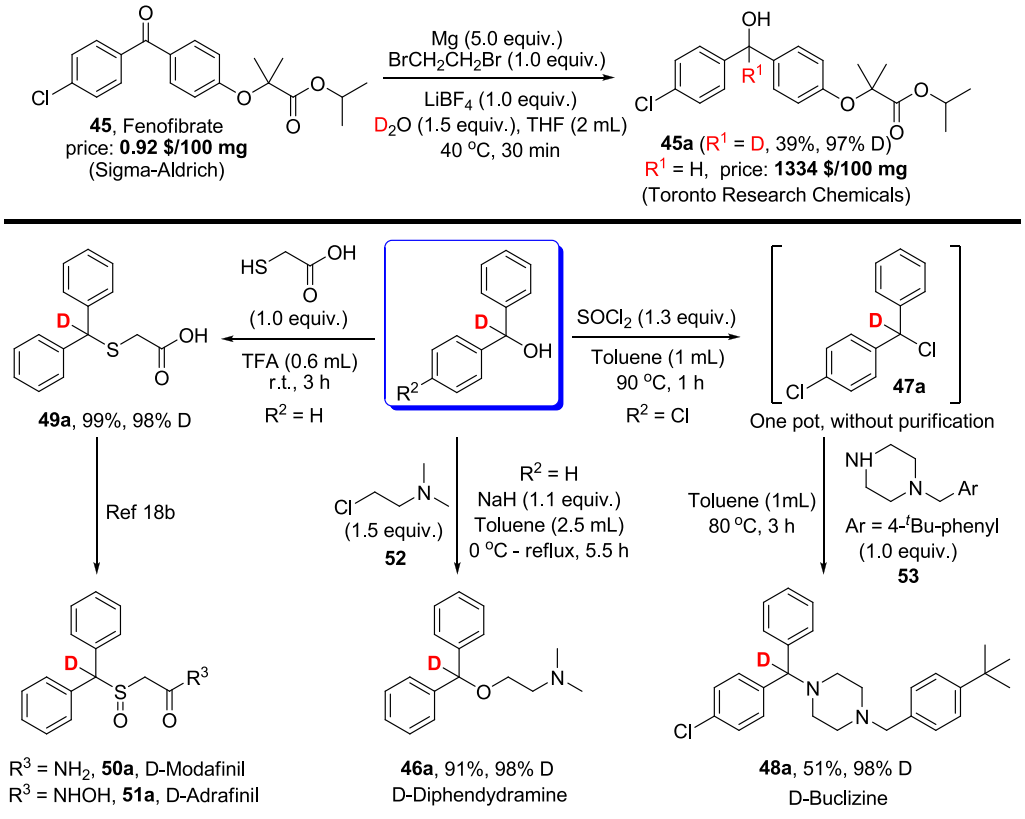

Figure 4. Synthetic applications to deuterium-containing drugs and precursors.

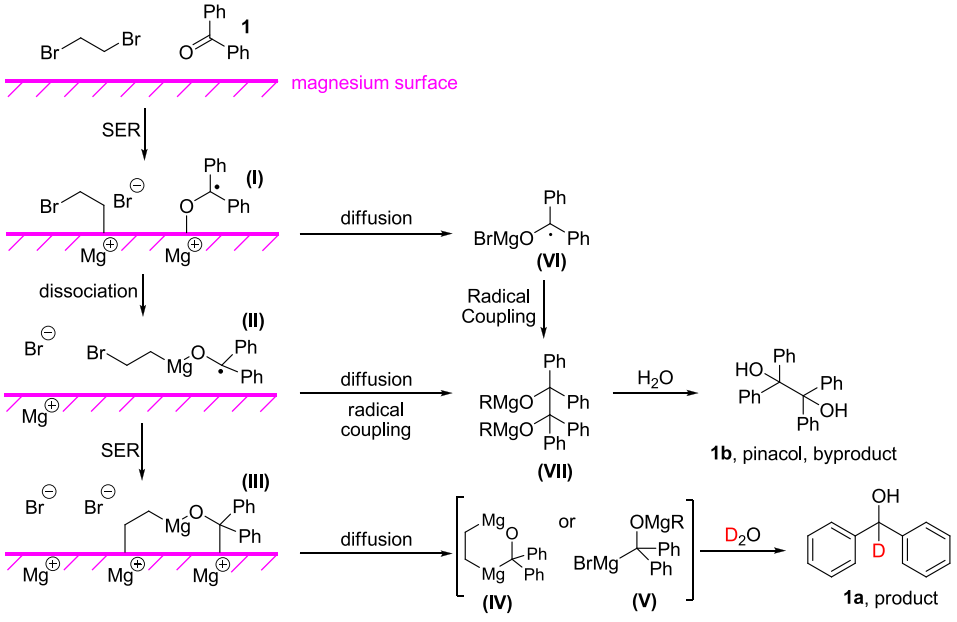

Figure 5. Proposed mechanism for the reductive deuteration of ketones.

and practical method for the synthesis of deuterium-containing or deuterium-modified drugs.

The mechanism of the reductive deuteration of carbonyl compounds with magnesium as a reducing agent was reported previously to proceed by a SER to give a radical anion. A pinacol adduct was obtained by rapid dimerization of the radical anion in the absence of interaction with an added proton source.[19] The desired alcohol was formed by protonation of the carbanion obtained by a further SER of the radical anion in the presence of a large excess of the proton source. In our method, only 1.5 equiv of the deuterium source (D_2O) is required for the efficient formation of the desired α-deuterated alcohols, and the use of alkyl bromides other than 1,2-dibromoethane all failed to provide the product with high deuterium incorporation. These facts imply that a new reaction mode utilizing $BrCH_2CH_2Br$ might be involved. Inspired by the comprehensive theoretical study of the Grignard reagent formation,[20] we conceived that the reaction may proceed

https://dx.doi.org/10.1021/acs.orglett.9b04536
Org. Lett. XXXX, XXX, XXX−XXX

through a six-membered metallacyclic intermediate **IV** or noncyclic metal intermediate **V**. A plausible mechanism was proposed and depicted in Figure 5. First, SER of the carbonyl compound and $BrCH_2CH_2Br$ proceeded on the magnesium surface to afford a radical anion **I** and an anchored Grignard reagent, respectively. Followed by dissociation of **II** from the metal surface, a second SER can afford the anchored metalated intermediate **III**, which will lead to the diffusion of intermediate **IV** or **V**. The desired α-deuterated alcohol is produced upon deuteration by D_2O. If the diffusion of the radicals **I** and **II** from the metal surface occurs prior to the SER process, a pinacol would be formed. We hypothesize that intermediate **IV** or **V** might be responsible for the reductive deuteration.

In conclusion, a practical method for the reductive deuteration of carbonyl compounds to α-deuterated alcohols with excellent deuterium incorporation is reported. Only 1.5 equiv of D_2O was required for the highly efficient transformation. This method features mild reaction conditions, good substrate scope, and excellent functional group tolerance. The importance of this methodology has been demonstrated by feasible reductive deuteration of fenofibrate and deuteration of drugs or drug precursors such as diphenhydramine, buclizine, modafinil, and adrafinil.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04536.

Experimental details, data, and spectra (PDF)

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Author Contributions

H.B. directed the investigations and prepared the manuscript. N.Z. and M.S. performed the synthetic experiments and analyzed the experimental data. N.Z., Y.L., and W.W. contributed to the discussion and preparation of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Key R&D Program of China (Grant 2017YFA0700103), the NSFC (Grants 21672213, 21871258, and 21922112), the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant XDB20000000), and the Haixi Institute of CAS (Grant CXZX-2017-P01) for financial support.

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https://dx.doi.org/10.1021/acs.orglett.9b04536
Org. Lett. XXXX, XXX, XXX−XXX