

Catalytic α -Selective Deuteration of Styrene Derivatives

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Supporting Information

ABSTRACT: We report an operationally simple protocol for the catalytic α -deuteration of styrenes. This process proceeds via the base-catalyzed reversible addition of methanol to styrenes in DMSO- d_6 solvent. The concentration of methanol is shown to be critical for high yields and selectivities over multiple competing side reactions. The synthetic utility of α -deuterated styrenes for accessing deuterium-labeled chiral benzylic stereocenters is demonstrated.

Tite-specific incorporation of deuterium into small mole-Cules is frequently practiced to access isotopically labeled compounds with broad utility in chemical research.¹ The increased strength of C-D bonds often imparts significant changes in reactivity compared to the C-H isotopologue.² In the context of medicinal chemistry, deuterium incorporation is a commonly used strategy to alter the absorption, distribution, metabolism and excretion (ADME) properties of drug candidates.^{1,3} Deuterium-labeled compounds also serve as tracers and analytical standards to help elucidate the mechanism and products of drug metabolism. In synthetic chemistry, deuterium-labeled compounds are widely used for kinetic isotope effect measurements and to track reaction pathways.⁴ Because of this widespread value, catalytic methods for the direct conversion of C-H bonds into C-D bonds with controlled regioselectivity are in high demand.

There have recently been significant advances made in selective hydrogen isotope exchange processes, especially at benzylic positions, adjacent to heteroatoms and on aromatic rings.^{5,6} Meanwhile, the deuteration of alkenes has also been recognized to have high value due to the synthetic and mechanistic utility of isotopically labeled olefins. Although a number of impressive metal-catalyzed deuteration methods have been reported for unactivated alkenes, extension to styrene derivatives is less developed.7 In addition to competing arene C-H activation processes, vinyl positional selectivity increases the challenges associated with selective styrene deuteration.⁸ Castarlenas and Oro have reported a Rhcatalyzed method that addresses these issues to selectively prepare $\beta_{,\beta}$ -dideuterated styrenes.⁹ Currently, however, an α selective styrene deuteration method remains undeveloped.

A large and continuously increasing number of enantioselective styrene functionalization reactions provide rapid access to benzylic stereocenters found in pharmaceuticals.¹⁰ Given that benzylic C-H bonds are prone to metabolic oxidation,¹¹ improved access to α -deuterated styrenes could harness the power of asymmetric functionalization methodologies to prepare chiral C–D isotopologues. Moreover, styrene- α - d_1 is among the most studied deuterium-labeled alkenes and increased access to its derivatives could facilitate additional mechanistic studies.¹² Commonly practiced routes to α deuterated styrenes involve multistep procedures and use expensive deuteride reagents (e.g., $LiAlD_4$) that limit functional group tolerance.¹³ An alternative reported method involves the selective hydroalumination of arylalkynes followed by addition of D₂O.¹⁴ We herein report a practical catalytic protocol for the α -selective deuteration of readily available styrene derivatives (Figure 1).



Figure 1. Catalytic α -selective deuteration of styrenes.

We recently reported that the organic superbase P_4 -t-Bu is a highly active catalyst for the anti-Markovnikov addition of alcohols to styrene derivatives, a reaction controlled by thermodynamic equilibria.¹⁵ Our subsequent mechanistic studies revealed that methanol (MeOH) addition in polar solvents leads to an unfavorable equilibrium constant for formation of the ether product. Using the addition of MeOH to 4-(trifluoromethyl)styrene (1) as a model reaction, we measured equilibrium yields of β -phenethyl ether 2 of 21% $(K_{eq} = 0.20)$ in *m*-xylene and 9% $(K_{eq} = 0.07)$ in dimethyl sulfoxide (DMSO) at 90 °C (Scheme 1a). This led us to hypothesize that if the forward reaction was run in DMSO- d_6 solvent, deuterium scrambling of MeOH to MeOD and reversible addition would result in α -selective styrene deuteration.¹⁶ In an initial experiment, P₄-t-Bu (10 mol %) catalyzed the α -selective deuteration of 1 in 88% yield with >99% deuterium incorporation (Scheme 1b). We found that KO-t-Bu had similar activity and this base was selected as the preferred catalyst for further studies.

We propose the α -deuteration process proceeds by the pathway outlined in Scheme 2. First, KO-t-Bu catalyzes MeO-H/D exchange with DMSO- d_6 and forms KOMe. KOMe then

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Scheme 1. Mechanistic Experiments Leading to the Discovery of Styrene α -Deuteration



Scheme 2. Possible Deuteration Pathway and Challenges



undergoes nucleophilic addition to the styrene with concomitant deuteration of the developing benzylic anion by MeOD, generating partially deuterated β -phenethyl ether 3. Finally, KOMe-catalyzed MeOH elimination from 3 forms the α deuterated styrene. Mechanistic studies (*vide infra*) support this sequence of events and the critical role of MeOH.¹⁸ We suspect that styrene deuteration is driven to completion by equilibration with excess DMSO- d_6 .¹⁹

Although conceptually straightforward, the α -deuteration pathway must outcompete multiple facile base-promoted reactions to be generally selective and useful for a broad styrene scope. For example, basic DMSO- d_6 solutions are known to readily deuterate weakly acidic arene C–H bonds.²⁰ A potentially larger challenge is avoiding base-catalyzed styrene polymerization or possible S_NAr side reactions.²¹ A final requirement for high α -deuterated styrene yield is that the equilibrium of the alcohol addition reaction must disfavor the β -phenethyl ether.

We found generally applicable reaction conditions using 1 or 3 equiv of MeOH and 10 mol % KO-t-Bu, although the optimal reaction temperature and time were adjusted empirically for each substrate.²² Typically, ¹H NMR monitoring of two initial reaction attempts using 1 and 3 equiv of MeOH allowed the identification of suitable conditions to obtain a preparative-scale isolated yield; a description of this process is provided in the Supporting Information.²³ Table 1 shows a diverse scope of styrene

Table 1. Styrene Scope for Catalytic α -Selective Deuteration^{*a*}



^{*a*}Isolated yields of alkene, % deuteration determined by ¹H and ²H NMR; reactions run between 50 and 130 °C at 0.5 M of alkene in DMSO- d_{6} , see Supporting Information. ^{*b*1}H NMR yield, isolated yields for product 1- α -d (52%) and 15- α -d (61%) were decreased due to volatility. ^{*c*}NaH used instead of KO-*t*-Bu.

derivatives that undergo 95% or greater α -deuteration with less than 5% total deuteration in other positions. Electron-poor to -neutral styrenes are suitable substrates, whereas electron-rich variants are not electrophilic enough to establish equilibrium under these conditions.¹⁵ Halogenated styrenes, including *ortho*-substituted bromide (4), chloride (5) and iodide (6) variants undergo selective α -deuteration while avoiding S_NAr reactions and aromatic deuteration. Ester (7), amide (8), (trifluoromethyl)thio (9) and stilbene (10) functional groups in the *meta-* and *para*-positions are also tolerated. Styrenes consisting of extended aromatic systems and heteroarenes, both of which contain relatively acidic arene C–H bonds, undergo selective α -deuteration.²⁴ This includes naphthalene (11 and 12), anthracene (13), pyridine (14 and 15), isoquinoline (16) and quinoline (17) vinyl arenes. We found that β -methylstyrene (18) undergoes α - and γ -deuteration, likely through a simple deprotonation process.²⁰ Meanwhile, a β -methoxystyrene (19) and a stilbene derivative (20) undergo selective deuteration. Additional substrates that were examined are provided in the Supporting Information.

We next performed reaction profile analysis studies to investigate the critical role of MeOH in enabling selective α deuteration over competing side reactions. Using styrene 14, we tracked α -deuterium incorporation (Figure 2a) and styrene







Figure 2. Reaction profile for the (a) deuteration rate and (b) mass balance for substrate **14** from Table 1 at 70 °C; values determined by ¹H NMR spectroscopy.

mass balance (14 + 14- α -*d*, Figure 2b) using varied quantities of MeOH (0.25, 0.5, and 1.0 equiv). The deuteration rate was notably faster when 0.25 equiv of MeOH was used, but the mass balance rapidly approached 0%.²⁵ In contrast, 1 equiv of MeOH led to complete α -deuteration while preserving the mass balance above 90%. The major side product of these reactions is the corresponding polystyrene, which is the only observed product when KO-*t*-Bu is used without any alcohol additive.²¹ These studies suggest that a critical concentration of alcohol is required for rapid deuteration of the developing benzylic anion by MeOD to outcompete anionic styrene polymerization.

Given the crucial role of the alcohol in this process, we reasoned that modifying its structure could overcome additional competing side reactions. Although *ortho*-halogenated styrenes undergo efficient α -deuteration (Table 1), we found that the more activated 2-chloro-3-vinylpyridine (21) primarily underwent S_NAr with only 21% α -deuteration of 21 when MeOH was used (see Supporting Information). We reasoned that a larger, but still nucleophilic, alcohol could promote α -deuteration over aromatic substitution. We discovered that use

of 1-cyclopropylethanol (22) and 18-crown-6 led to 96% α -deuteration in 63% yield (eq 1).²⁶ We expect this strategy could be utilized if other challenging substrates are encountered.



In addition to their value for mechanistic experiments, another utility of α -deuterated styrenes is their elaboration to deuterium-labeled chiral benzylic stereocenters of pharmaceutical relevance, positions frequently prone to metabolic oxidation.¹¹ To highlight this potential, Figure 3 shows three deuterium-labeled chiral compounds, including the pharmaceutical cinacalcet (23), that were rapidly prepared from substrates in Table 1.^{10a,27} We expect this simple catalytic deuteration protocol will find use in these and related applications.



Figure 3. Preparation of deuterium-labeled chiral compounds from α -deuterated styrenes in Table 1. "Isolated yield of product starting from α -deuterated styrene substrate; see Supporting Information for synthetic details.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b12874.

Experimental procedures and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(22) It is possible to use lower catalyst loadings of KO-t-Bu, although the reaction takes significantly longer to reach completion. For example, substrate $11-\alpha$ -d requires 4 h to reach 97% α -deuteration using 10 mol% KO-t-Bu at 130 °C according to the general procedure, while 5 mol% KO-t-Bu required 24 h under identical conditions.

(23) The reaction must be conducted under inert atmosphere according to the general procedure in the Supporting Information. Reactions run in the presence of oxygen (1 atm balloon) resulted in no α -deuteration. The deuteration reaction of substrate 14 in the

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presence of 1 and 5 equiv of water resulted in 94% and 65% α deuteration, respectively. These studies indicate small quantities of water are tolerated, although excess water is not.

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