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Catalytic α-Selective Deuteration of Styrene Derivatives

Thomas R. Puleo, Alivia J. Strong and Jeffrey S. Bandar*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States

Supporting Information Placeholder

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.

Site-specific incorporation of deuterium into small molecules 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] Due to this widespread value, catalytic methods for the direct conversion of C–H bonds into C–D bonds with controlled regioselectivity are in high demand.[5]

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 Rh-catalyzed method that addresses these issues to selectively prepare β,β-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 amongst 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 D_2O.[14] We herein report a practical catalytic protocol for the α-selective deuteration of readily available styrene derivatives (Figure 1).

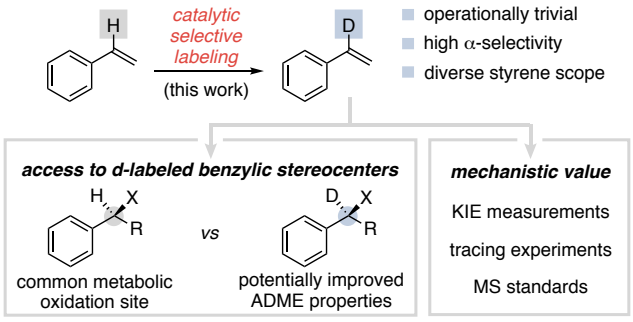
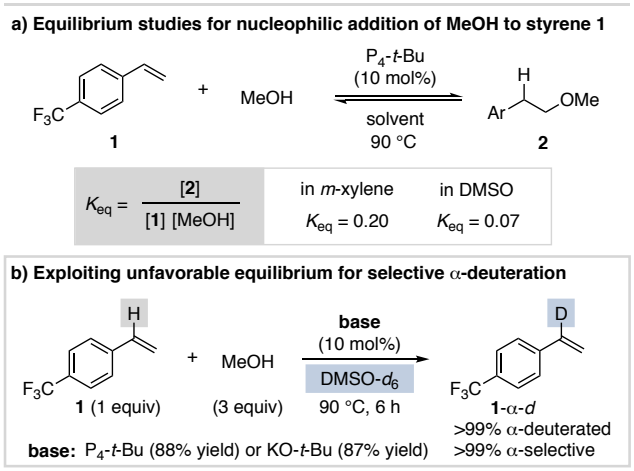


Figure 1. Catalytic α-selective deuteration of styrenes.

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

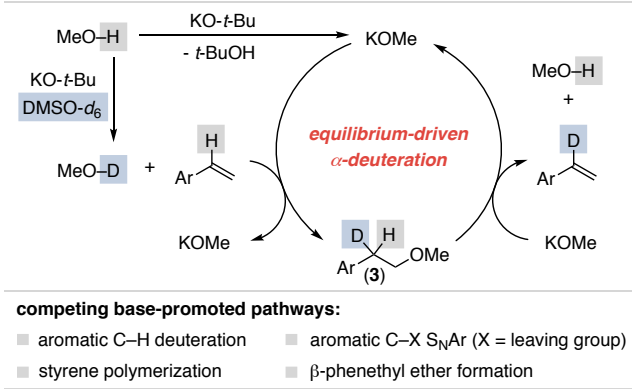
measured equilibrium yields of β-phenethyl ether **2** of 21% (K_{eq} = 0.20) in *m*-xylene and 9% (K_{eq} = 0.07) in dimethylsulfoxide (DMSO) at 90 °C (Scheme 1a). This led us to hypothesize that if the forward reaction was run in DMSO-d_6 solvent, deuterium scrambling of MeOH to MeOD and reversible addition would result in α-selective styrene deuteration.[16] In an initial experiment, P_4-*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.[17]

Scheme 1. Mechanistic experiments leading to the discovery of styrene α-deuteration.



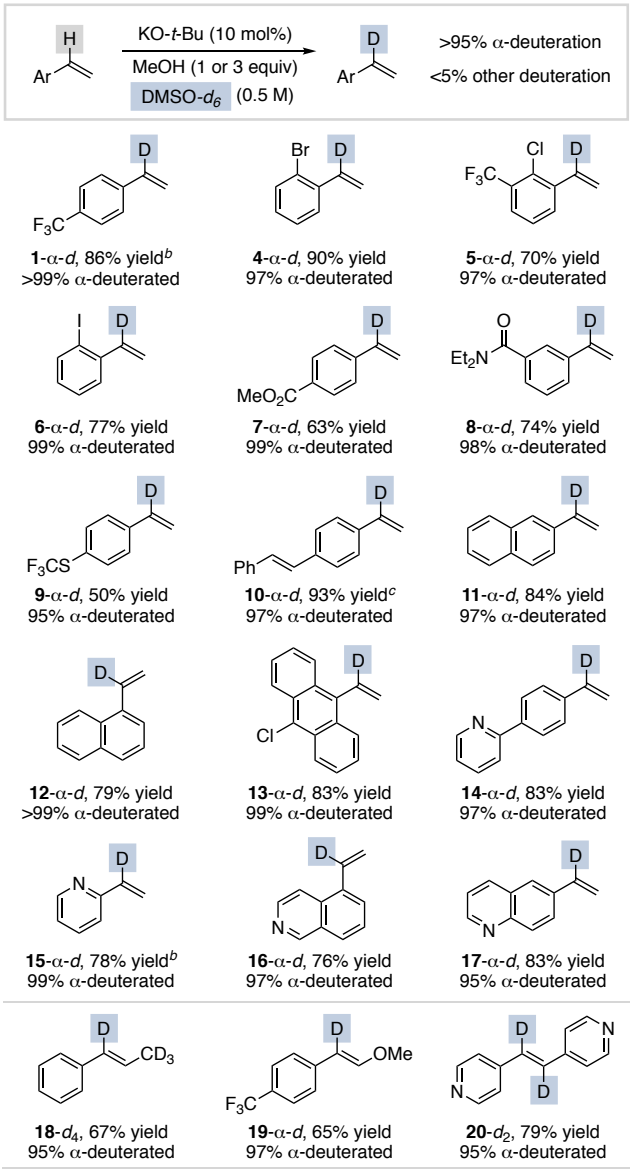
We propose the α-deuteration process proceeds by the pathway outlined in Scheme 2. First, KO-*t*-Bu catalyzes MeO–H/D exchange with DMSO-d_6 and forms KOMe. KOMe then undergoes nucleophilic addition to the styrene with concomitant deuteration of the developing benzylic anion by MeOD, generating partially 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]

Scheme 2. Possible deuteration pathway and challenges.



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.

Table 1. Styrene scope for catalytic α-selective deuteration.[a]



[a] Isolated yields of alkene, % deuteration determined by ^{1}H and ^{2}H NMR; reactions run between 50-130 °C at 0.5M 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.

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, ^{1}H 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 derivatives that undergo greater than 95% 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.

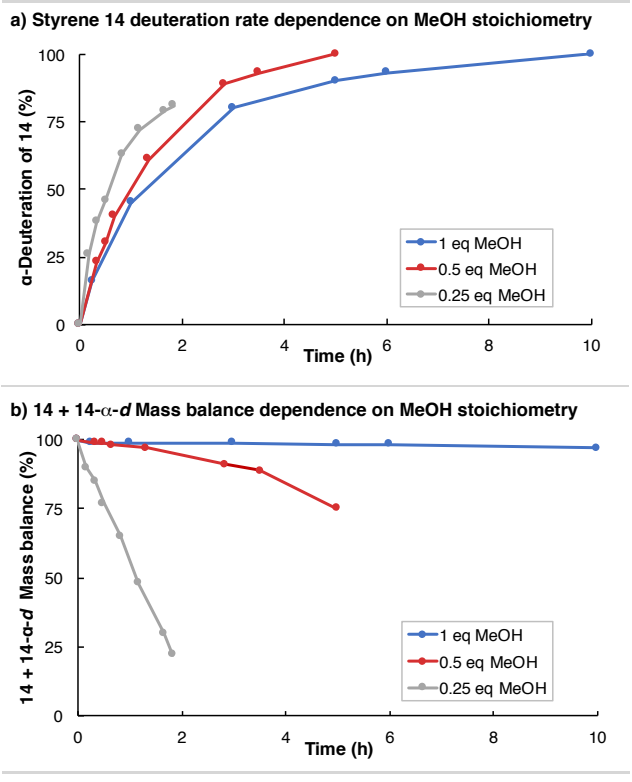
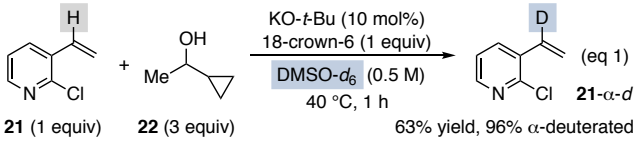


Figure 2. Reaction profile for the (a) deuteration rate and (b) mass balance for substrate **14** from Table 1 at 70 °C; values determined by ^{1}H NMR spectroscopy.

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 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 (equation 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.

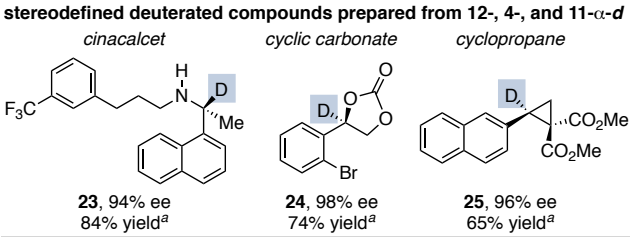


Figure 3. Preparation of deuterium-labeled chiral compounds from α-deuterated styrenes in Table 1. [a] Isolated yield of product starting from α-deuterated styrene substrate; see Supporting Information for synthetic details.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and characterization data for all compounds (PDF).

AUTHOR INFORMATION

Corresponding Author

*jeff.bandar@colostate.edu

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For general reviews on the applications of deuterium-labeled compounds, see: (a) Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid, M. Deuterium- and Tritium-Labelled Compounds: Applications in the Life Sciences. *Angew. Chem. Int. Ed.* **2017**, *57*, 1758. (b) *Isotope Effects in Chemistry and Biology*; Kohen, A.; Limbach, H.-H., Eds; CRC Press: Boca Raton, FL, 2006.

(2) (a) Wiberg, K. B. The Deuterium Isotope Effect. *Chem. Rev.* **1955**, *55*, 713. (b) O'Ferrall, R. A. M. A pictorial representation of zero-point energy and tunnelling contributions to primary hydrogen isotope effects. *J. Phys. Org. Chem.* **2010**, *23*, 572.

(3) For reviews and discussions of the use of deuterium in medicinal chemistry, see: (a) Elmore, C. S.; Bragg, R. A. Isotope chemistry; a useful tool in the drug discovery arsenal. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 167. (b) Grant, T. G. Using Deuterium in Drug Discovery: Leaving the Label in the Drug. *J. Med. Chem.* **2014**, *57*, 3595. (c) Harbeson, S. L.; Tung, R. D. Chapter 24 - Deuterium in Drug Discovery and Development. *Annu. Rep. Med. Chem.* **2011**, *46*, 403. (d) Liu, J. F.; Harbeson, S. L.; Brummel, C. L.; Tung, R.; Silverman, R.; Doller, D. Chapter Fourteen - A Decade of Deuteration in Medicinal Chemistry. *Annu. Rep. Med. Chem.* **2017**, *50*, 519. (e) Mutlib, A. E. Application of Stable Isotope-Labeled Compounds in Metabolism and in Metabolism-Mediated Toxicity Studies. *Chem. Res. Toxicol.* **2008**, *21*, 1672. (f) Tung, D. Deuterium medicinal chemistry comes of age. *Future Med. Chem.* **2016**, *8*, 491.

(4) For selected reviews on the use of deuterium-labeled compounds in mechanistic studies, see: (a) Anslyn, E. V.; Dougherty, D. A. In *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006; pp 421-441 and 477-478. (b) Scheppele, S. E. Kinetic isotope effects as a valid measure of structure-reactivity relations. Isotope effects and nonclassical theory. *Chem. Rev.* **1972**, *72*, 511. (c) Westaway, K. C. Determining transition state structure using kinetic isotope effects. *J. Label. Compd. Radiopharm.* **2007**, *50*, 989. (d) Westheimer, F. H. The Magnitude of the Primary Kinetic Isotope Effect for Compounds of Hydrogen and Deuterium. *Chem. Rev.* **1961**, *61*, 265. (e) Westaway, K. C. Using kinetic isotope effects to determine the structure of the transition states of S_N2 reactions. *Adv. Phys. Org. Chem.* **2006**, *41*, 217. (f) Gómez-Gallego, M.; Sierra, M. A. Kinetic Isotope Effects in the Study of Organometallic Reaction Mechanisms. *Chem. Rev.* **2011**, *111*, 4857. (g) Meek, S. J.; Pitman, C. L.; Miller, A. J. M. Deducing Reaction Mechanism: A Guide for Students, Researchers, and Instructors. *J. Chem. Ed.* **2016**, *93*, 275.

(5) For reviews on hydrogen isotope exchange reactions, see: (a) Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid, M. C–H Functionalisation for Hydrogen Isotope Exchange. *Angew. Chem. Int. Ed.* **2018**, *57*, 3022. (b) Atzrodt, J.; Derdau, V.; Fey, T.; Zimmerman, J. The Renaissance of H/D Exchange. *Angew. Chem. Int. Ed.* **2007**, *46*, 7744. (c) Junk, T.; Catallo, W. J. Hydrogen isotope exchange reactions involving C–H (D, T) bonds. *Chem. Soc. Rev.* **1997**, *26*, 401. (d) Sattler, A. Hydrogen/Deuterium (H/D) Exchange Catalysis in Alkanes. *ACS Catal.* **2018**, *8*, 2296. (e) Hesk, D.; Lavey, C. F.; McNamara, P. Tritium labelling of pharmaceuticals by metal-catalysed exchange methods. *J. Label. Compd. Radiopharm.* **2010**, *53*, 722. (f) Lockley, W. J. S.; Heys, J. R. Metal-catalysed hydrogen isotope exchange labelling: a brief overview. *J. Label. Compd. Radiopharm.* **2010**, *53*, 635. (g) Sawama, Y.; Monguchi, Y.; Sajiki, H. Efficient H–D Exchange Reactions Using Heterogeneous Platinum-Group Metal on Carbon–H_2–D_2O System. *Synlett* **2012**, *23*, 959.

(6) For selected examples of recently reported hydrogen isotope exchange processes, see: (a) Loh, Y. Y.; Nagao, K.; Hoover, A. J.; Hesk, D.; Rivera, N. R.; Colletti, S. L.; Davies, I. W.; MacMillan, D. W. C. Photoredox-catalyzed deuteration and tritiation of pharmaceutical compounds. *Science* **2017**, *358*, 1182. (b) Yu, R. P.; Hesk, D.; Rivera, N.; Pelczer, I.; Chirik, P. J. Iron-catalysed tritiation of pharmaceuticals. *Nature* **2016**, *529*, 195. (c) Palmer, W. N.; Chirik, P. J. Cobalt-Catalyzed Stereoretentive Hydrogen Isotope Exchange of $C(sp^3)$–H Bonds. *ACS Catal.* **2017**, *7*, 5674. (d) Yang, H.; Zarate, C.; Palmer, W. N.; Rivera, N.; Hesk, D.; Chirik, P. J. Site-Selective Nickel-Catalyzed Hydrogen Isotope Exchange in *N*-Heterocycles and Its Application to the Tritiation of Pharmaceuticals. *ACS Catal.* **2018**, *8*, 10210. (e) Koniarczyk, J. L.; Hesk, D.; Overgard, A.; Davies, I. W.; McNally, A. A General Strategy for Site-Selective Incorporation of Deuterium and Tritium into Pyridines, Diazines, and Pharmaceuticals. *J. Am. Chem. Soc.* **2018**, *140*, 1990. (f) Hale, L. V. A.; Szymczak, N. K. Stereoretentive Deuteration of α-Chiral Amines with D_2O. *J. Am. Chem. Soc.* **2016**, *138*, 13489. (g) Neubert, L.; Michalik, D.; Bähn, S.; Imm, S.; Neumann, H.; Atzrodt, J.; Derdau, V.; Holla, W.; Beller, M. Ruthenium-Catalyzed Selective α,β-Deuteration of Bioactive Amines. *J. Am. Chem. Soc.* **2012**, *134*, 12239. (h) Valero, M.; Weck, R.; Güssregen, S.; Atzrodt, J.; Derdau, V. Highly Selective Directed Iridium-Catalyzed Hydrogen Isotope Exchange Reactions of Aliphatic Amides. *Angew. Chem. Int. Ed.* **2018**, *57*, 8159. (i) Kerr, W. J.; Mudd, R. J.; Reid, M.; Atzrodt, J.; Derdau, V. Iridium-Catalyzed Csp^3–H Activation for Mild and Selective Hydrogen Isotope Exchange. *ACS Catal.* **2018**, *8*, 10895.

(7) For examples of catalytic alkene deuteration, see: (a) Zhou, J.; Hartwig, J. F. Iridium-Catalyzed H/D Exchange at Vinyl Groups without Olefin Isomerization. *Angew. Chem. Int. Ed.* **2008**, *47*, 5783. (b) Erdogan, G.; Grotjahn, D. B. Mild and Selective Deuteration and Isomerization of Alkenes by a Bifunctional Catalyst and Deuterium Oxide. *J. Am. Chem. Soc.* **2009**, *131*, 10354. (c) Lenges, C. P.; White, P. S.; Brookhart, M. Hydrogen/Deuterium Exchange Reactions and Transfer Hydrogenations Catalyzed by $[C_5Me_5Rh(olefin)_2]$ Complexes: Conversion of Alkoxysilanes to Silyl Enolates. *J. Am. Chem. Soc.* **1999**, *121*, 4385. (d) Faller, J. W.; Smart, C. J. Stereoelective Vinylic C-H Activation by a Homogeneous Iridium Catalyst. *Organometallics* **1989**, *8*, 602. (e) Bechtoldt, A.; Ackermann, L. Ruthenium(II)biscarboxylate-Catalyzed Hydrogen-Isotope Exchange by Alkene C–H Activation. *ChemCatChem*, doi: 10.1002/cctc.201801601. (f) Smarun, A. V.; Petković, M.; Shchepinov, M. S.; Vidović, D. Site-Specific Deuteration of Polyunsaturated Alkenes. *J. Org. Chem.* **2017**, *82*, 13115.

(8) For examples of deuteration of styrene derivatives, see: (a) Hatano, M.; Nishimura, T.; Yorimitsu, H. Selective H/D Exchange at Vinyl and Methylidene Groups with D_2O Catalyzed by an Iridium Complex. *Org. Lett.* **2016**, *18*, 3674. (b) Rybtchinski, B.; Cohen, R.; Ben-David, Y.; Martin, J. M. L.; Milstein, D. Aromatic vs Aliphatic C-H Bond Activation by Rhodium(I) as a Function of Agostic Interactions: Catalytic H/D Exchange between Olefins and Methanol or Water. *J. Am. Chem. Soc.* **2003**, *125*, 11041. (c) Corberán, R.; Sanaú, M.; Peris, E. Highly Stable Cp*-Ir(III) Complexes with *N*-Heterocyclic Carbene Ligands as C-H Activation Catalysts for the Deuteration of Organic Molecules. *J. Am. Chem. Soc.*

2006, *128*, 3974. (d) Tse, S. K. S.; Xue, P.; Lin, Z.; Jia, G. Hydrogen/Deuterium Exchange Reactions of Olefins with Deuterium Oxide Mediated by the Carbonylchlorohydrido-tris(triphenylphosphine)-ruthenium(II) Complex. *Adv. Synth. Catal.* **2010**, *352*, 1512.

(9) (a) Giuseppe, A. D.; Castarlenas, R.; Pérez-Torrente, J. J.; Lahoz, F. J.; Polo, V.; Oro, L. A. Mild and Selective H/D Exchange at the β Position of Aromatic α-Olefins by N-Heterocyclic Carbene–Hydride–Rhodium Catalysts. *Angew. Chem. Int. Ed.* **2011**, *50*, 3938. (b) Giuseppe, A. D.; Castarlenas, R.; Pérez-Torrente, J. J.; Lahoz, F. J.; Oro, L. A. Hydride-Rhodium(III)-N-Heterocyclic Carbene Catalysts for Vinyl-Selective H/D Exchange: A Structure–Activity Study. *Chem. Eur. J.* **2014**, *20*, 8391.

(10) A large number of enantioselective styrene functionalization reactions exist; for selected reviews and examples of a subset that demonstrate the diversity of these reactions, see: (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation *Chem. Rev.* **1994**, *94*, 2483. (b) Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L. Copper Hydride Catalyzed Hydroamination of Alkenes and Alkynes. *Angew. Chem. Int. Ed.* **2016**, *55*, 48. (c) Degennaro, L.; Trinchera, P.; Luisi, R. Recent Advances in the Stereoselective Synthesis of Aziridines. *Chem. Rev.* **2014**, *114*, 7881. (d) Han, J. W.; Hayashi, T. Palladium-catalyzed asymmetric hydrosilylation of styrenes with trichlorosilane. *Tetrahedron: Asymmetry* **2014**, *25*, 479. (e) Jui, N. T.; Garber, J. A. O.; Finelli, F. G.; MacMillan, D. W. C. Enantioselective Organo-SOMO Cycloadditions: A Catalytic Approach to Complex Pyrrolidines from Olefins and Aldehydes. *J. Am. Chem. Soc.* **2012**, *134*, 11400. (f) Friis, S. D.; Pirnot, M. T.; Buchwald, S. L. Asymmetric Hydroarylation of Vinylarenes Using a Synergistic Combination of CuH and Pd Catalysis *J. Am. Chem. Soc.* **2016**, *138*, 8372. (g) Wong, O. A.; Shi, Y. Organocatalytic Oxidation. Asymmetric Epoxidation of Olefins Catalyzed by Chiral Ketones and Iminium Salts. *Chem. Rev.* **2008**, *108*, 3958. (h) Chanthamath, S.; Iwasa, S. Enantioselective Cyclopropanation of a Wide Variety of Olefins Catalyzed by Ru(II)–Pheox Complexes. *Acc. Chem. Res.* **2016**, *49*, 2080.

(11) For reviews and examples, see: (a) Zhang, Z.; Tang, W. Drug metabolism in drug discovery and development. *Acta Pharmacol. Sin. B* **2018**, *8*, 721. (b) Silverman, R. B., Holladay, M. W. *The Organic Chemistry of Drug Design and Drug Action*; Academic Press: San Diego, CA, 2014; pp 357-422. (c) Guengerich, F. P. Common and Uncommon Cytochrome P450 Reactions Related to Metabolism and Chemical Toxicity. *Chem. Res. Toxicol.* **2001**, *14*, 611. (d) Nelson, S. D.; Trager, W. F. The Use of Deuterium Isotope Effects to Probe the Active Site Properties, Mechanism of Cytochrom P450-Catalyzed Reactions, and Mechanisms of Metabolically Dependent Toxicity. *Drug Metab. Dispos.* **2003**, *31*, 1481. (e) Usmani, K. A.; Chen, W. G.; Sadeque, A. J. M. Identification of Human Cytochrome P450 and Flavin-Containing Monooxygenase Enzymes Involved in the Metabolism of Lorcaserin, a Novel Selective Human 5-Hydroxytryptamine 2C Agonist. *Drug Metab. Dispos.* **2012**, *40*, 761. (f) Shetty, H. U.; Nelson, W. L. Chemical aspects of metoprolol metabolism. Asymmetric synthesis and absolute configuration of the 3-[4-(1-hydroxy-2-methoxyethyl)phenoxy]-1-(isopropylamino)-2-propanols, the diastereomeric benzylic hydroxylation metabolites. *J. Med. Chem.* **1988**, *31*, 55. (g) Sun, H.; Scott, D. O. Structure-based Drug Metabolism Predictions for Drug Design. *Chem. Biol. Drug Des.* **2010**, *75*, 3.

(12) For selected examples of α-deuterated styrenes used in mechanistic studies, see: (a) Maji, A.; Reddi, Y.; Sunoj, R. B.; Maiti, D. Mechanistic Insights on Orthogonal Selectivity in Heterocycle Synthesis. *ACS Catal.* **2018**, *8*, 10111. (b) Fang, X.; Yu, P.; Cerai, G. P.; Morandi, B. Unlocking Mizoroki–Heck-Type Reactions of Aryl Cyanides Using Transfer Hydrocyanation as a Turnover-Enabling Step. *Chem. Eur. J.* **2016**, *22*, 15629. (c) Fra, L.; Millán, A.; Souto, J. A.; Muñiz, K. Indole Synthesis Based On A Modified Koser Reagent. *Angew. Chem. Int. Ed.* **2014**, *53*, 7349. (d) Cornell, C. N.; Sigman, M. S. Discovery of and Mechanistic Insight into a Ligand-Modulated Palladium-Catalyzed Wacker Oxidation of Styrenes Using TBHP. *J. Am. Chem. Soc.* **2005**, *127*, 2796. (e) Walker, K. L.; Dornan, L. M.; Zare, R. N.; Waymouth, R. M.; Muldoon, M. J. Mechanism of Catalytic Oxidation of Styrenes with Hydrogen Peroxide in the Presence of Cationic Palladium(II) Complexes. *J. Am. Chem. Soc.* **2017**, *139*, 12495. (f) Pryor, W. A.; Henderson, R. W.; Patsiga, R. A.; Carroll, N. Hydrogen Secondary Isotope Effects on the Radical Polymerization of Styrene. *J. Am. Chem. Soc.* **1966**, *88*, 1199.

(13) For examples of these synthetic routes, see: (a) references 12c and 12e (b) Gülak, S.; Gieshoff, T. N.; von Wangelin, A. J. Olefin-Assisted Iron-Catalyzed Alkylation of Aryl Chlorides. *Adv. Synth. Catal.* **2013**, *355*, 2197. (c) García-Rubín, S.; González-Rodríguez, C.; García-Yebra, C.; Varela, J. A.; Esteruelas, M. A.; Saá, C. Dihydrobiphenylenes through Ruthenium-Catalyzed [2+2+2] Cycloadditions of *ortho*-Alkenylarylacetylenes with Alkynes. *Angew. Chem. Int. Ed.* **2014**, *53*, 1841. (d) Vassilikogiannakis, G.; Orfanopoulos, M. Stereochemistry and Isotope Effects of the [2 + 2] Photocycloadditions of Arylalkenes to C_{60}. A Stepwise Mechanism. *J. Am. Chem. Soc.* **1997**, *119*, 7394.

(14) (a) Gao, F.; Hoveyda, A. H. α-Selective Ni-Catalyzed Hydroalumination of Aryl- and Alkyl-Substituted Terminal Alkynes: Practical Syntheses of Internal Vinyl Aluminums, Halides, or Boronates. *J. Am. Chem. Soc.* **2010**, *132*, 10961. For an additional alternative route, see: (b) Kerr, W. J.; Morrison, A. J.; Pazicky, M.; Weber, T. Modified Shapiro Reactions with Bismesitylmagnesium As an Efficient Base Reagent. *Org. Lett.* **2012**, *14*, 2250.

(15) (a) Luo, C.; Bandar, J. S. Superbase-Catalyzed anti-Markovnikov Alcohol Addition Reactions to Aryl Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 3547. (b) Luo, C.; Bandar, J. S. Synthesis of β-Phenethyl Ethers by Base-Catalyzed Alcohol Addition Reactions to Aryl Alkenes. *Synlett* **2018**, *29*, 2218.

(16) For a related approach applied to acrylate derivatives, see: (a) Mathias, L. J.; Colletti, R. F. Facile synthesis of α-deuterated acrylates and activated vinyls. *Macromolecules* **1988**, *21*, 857. (b) Zinn, M. F.; Harris, T. M.; Hill, D. G.; Hauser, C. R. Base-catalyzed Hydrogen Deuterium Exchange at the α-Carbon of Ethyl Cinnamate and Certain Related Compounds. *J. Am. Chem. Soc.* **1963**, *85*, 71.

(17) Use of CD_3OD as a solvent provided no α-deuteration.

(18) Intermediate **3** is frequently observed by ^{1}H NMR as a minor side product for substrates in Table 1. Upon heating, the concentration of this intermediate decreases and an increase of α-deuterated styrene is observed. These observations support the proposed addition/elimination pathway; however, it is possible that a direct α-deprotonation process may provide a pathway for α-deuteration; see: (a) Mori, H.; Matsuo, T.; Yoshioka, Y.; Katsumura, S. Highly Activated Vinyl Hydrogen in a Significantly Twisted Styrene. *J. Org. Chem.* **2006**, *71*, 9004. (b) Tricotet, T.; Fleming, P.; Cotter, J.; Hogan, A.-M. L.; Strohmann, C.; Gessner, V. H.; O'Shea, D. F. Selective Vinyl C–H Lithiation of cis-Stilbenes. *J. Am. Chem. Soc.* **2009**, *131*, 3142.

(19) We also considered that a primary KIE in the elimination of MeOH from ether **3** could contribute to the high α-deuterium incorporation. Subjection of α-deuterated styrenes to basic DMSO solutions resulted in α-protium incorporation at a rate identical to styrene α-deuterium incorporation in basic DMSO-d_6 solutions. This result suggests that a KIE in the elimination step is not responsible for high α-deuterium incorporation.

(20) For examples of base-catalyzed aromatic deuteration, see: (a) Hu, Y.; Liang, L.; Wei, W.; Sun, X.; Zhang, X.; Yan, M. A convenient synthesis of deuterium labeled amines and nitrogen heterocycles with KO*t*-Bu/DMSO-d_6. *Tetrahedron* **2015**, *71*, 1425. (b) Patel, M.; Saunthwal, R. K.; Verma, A. K. Base-Mediated Deuteration of Organic Molecules: A Mechanistic Insight. *ACS Omega* **2018**, *3*, 10612. (c) Hirono, Y.; Kobayashi, K.; Yonemoto, M.; Kondo, Y. Metal-free deprotonative functionalization of heteroaromatics using organic superbase catalyst. *Chem. Commun.* **2010**, *46*, 7623.

(21) (a) *Anionic Polymerization: Principles, Practice, Strength, Consequences and Applications*; Hadjichristidis, N.; Hirao, A., Eds; Springer: Tokyo, Japan, 2015. (b) Baskaran, D.; Müller, A. H. E. Anionic Vinyl Polymerization. In *Controlled and Living Polymerization: From Mechanisms to Applications*; Müller, A. H. E., Matyjaszewski, K., Eds.; Wiley-VCH Verlag GmbH & KGaA: Weinheim, 2009; pp 1–56. (c) Ntetsikas, K.; Alzahrany, Y.; Polymeropoulos, G.; Bilalis, P.; Gnanou, Y.; Hadjichristidis, N. Anionic Polymerization of Styrene and 1,3-Butadiene in the Presence of Phosphazene Superbases. *Polymers* **2017**, *9*, 538. (d) Hurley, S. A.; Tait, P. J. T. Anionic polymerization initiated by lithium diethylamide in organic

solvents. III. Investigation of the polymerization of styrene. *J. Polym. Sci. A*, **1976**, *14*, 1565.

(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-*α-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 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.

(24) Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. What are the pK_a values of C–H bonds in aromatic heterocyclic compounds in DMSO? *Tetrahedron* **2007**, *63*, 1568.

(25) We hypothesize that excess MeOH may participate in hydrogen-bonding to the active potassium alkoxide ion pair, thus decreasing alkoxide nucleophilicity; mechanistic studies concerning this issue are ongoing.

(26) When *t*-BuOH and other tertiary alcohols were examined for this reaction, incomplete α-deuteration and low mass balance of the styrene was observed.

(27) See the Supporting Information for details of the synthetic routes to **23**-**25**. (a) Niu, D.; Buchwald, S. L. Design of Modified Amine Transfer Reagents Allows the Synthesis of α-Chiral Secondary Amines via CuH-Catalyzed Hydroamination. *J. Am. Chem. Soc.* **2015**, *137*, 9716. (b) Sapeta, K.; Kerr, M. A. The Cycloaddition of Nitrones with Homochiral Cyclopropanes. *J. Org. Chem.* **2007**, *72*, 8597.