Published in final edited form as:

Nature. 2020 May ; 581(7808): 288–293. doi:10.1038/s41586-020-2268-y.

Preparation of Cyclohexene Isotopologues and Stereoisotopomers from Benzene

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Abstract

The hydrogen isotopes deuterium (D) and tritium (T) have become essential tools of chemistry, biology, and medicine.[1] Beyond their widespread use in spectroscopy, mass spectrometry, and mechanistic and pharmacokinetic studies, there has been considerable interest in incorporating deuterium into drug molecules.[1] The deuterium kinetic isotope effect (DKIE), which compares the rate of a chemical reaction for a compound to its deuterated counterpart, can be dramatic.[1–3] The strategic replacement of hydrogen with deuterium can affect both the rate of metabolism and distribution of metabolites for a compound,[4] improving the efficacy and safety of the drug. Deutetrabenazine, a promising treatment for Huntington's disease,[5] recently became the first deuterated drug to win FDA-approval.The pharmacokinetics of a deuterated compound depend on the location(s) of D. While methods currently exist for deuterium incorporation at both early and late stages of a drug's synthesis,[6–7] these processes are often unselective and the stereoisotopic purity can be difficult to measure.[7–8] Here, we describe the preparation of stereoselectively deuterated building blocks for pharmaceutical research. As a proof of concept, we demonstrate a four-step conversion of benzene to cyclohexene with varying degrees of D incorporation, as bound to a tungsten complex. Using different combinations of deuterated and proteated acid and hydride reagents, the deuterated positions can be precisely controlled on the cyclohexene ring. In total, 52 unique stereoisotopomers of cyclohexene are available, in the form of ten different isotopologues. This concept can be extended to prepare discrete stereoisotopomers of functionalized cyclohexenes. Such systematic methods for the preparation of pharmacologically active compounds as discrete stereoisotopomers could improve pharmacological and toxicological

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Author Contributions: WDH, JAS, and KBW conceived the project. KDW, WDH, and JAS designed the experiments. JAS and KSW prepared samples and collected NMR and HRMS data. DD carried out X-ray molecular structure determinations. BP, PK, and RS conceived of and ran the rotational spectroscopy experiments, EKP and KSW carried out DFT calculations. JAS and WDH wrote the manuscript. XW collected and processed neutron diffraction data.

Online content:

Full synthetic procedures, spectra, compound characterizations, DFT calculations, and supplementary figures and tables.

The authors declare no competing interests.

properties of drugs and provide new mechanistic information related to their distribution and metabolism in the body.

Typically, hydrogenation of benzene using D_2 gas leads to isotopologue mixtures of cyclohexane.[10–12] However, Taube et al. demonstrated that the complex $[Os(NH_3)_5(\eta^2\text{-benzene})]^{2+}$ could be deuterated to form a single stereoisotopomer of $[Os(NH_3)_5(\eta^2\text{-cyclohexene-}d_4)]^{2+}$ using D_2 and a Pd/C catalyst.[13] We posited that benzene bound in this manner could also be converted to cyclohexene using four well-defined additions of two protons and two hydrides, passing through an η^2-1,3-cyclohexadiene intermediate (Fig. 1). If these reactions could be performed regio- and stereoselectively, one could access a diverse set of isotopologues and even stereoisotopomers of cyclohexene using various combinations of proteated and deuterated reagents.

The dearomatization agent {WTp(NO)(PMe_3)} is considerably more activating than its osmium predecessor.[9] Strong **π**-backbonding renders arene and diene complexes of this system highly nucleophilic, and resistant to substitution.[9] Furthermore, this system displays significant electronic asymmetry, and the benzene complex WTp(NO)(PMe_3)(η^2-benzene) (**1**) can be prepared on a multi-gram scale,[14] and in enantioenriched form.[15] Treatment of an acetone-d_6 solution of **1** with diphenylammonium triflate (DPhAT, $pK_a \sim 0$) at −30 °C affords its clean conversion to the η^2-benzenium complex [WTp(PMe_3)(NO)(η^2-C_6H_7)](OTf) (**2**; Fig. 2). Using chilled diethyl ether as a precipitating solvent, **2** can be isolated from dichloromethane in 86% yield (1.9 g). As an acetonitrile solution, the η^2-benzenium complex **2** is moderately stable at room temperature but soon decomposes ($t_{1/2} \sim 6$ min). At 0°C, however, **2** exists in equilibrium with its diastereomer **3** in a 10:1 ratio (Fig. 2) and persists for three hours without significant decomposition. The major isomer (**2**) is formed with the metal binding two internal carbons of the five-carbon **π**-system, and with the newly formed sp^3 carbon distal to the PMe_3 ligand. The minor isomer (**3**) is bound at a terminus of the **π**-system with the sp^3 carbon proximal to the phosphine. Proton NMR data and DFT calculations (Supplementary materials; Fig S1–S3) of these η^2-benzenium complexes (**2**, **3**) suggest that they are similar in structure to complexes of the form [WTp(NO)(PMe_3)(η^2-allyl)]$^+$,[16] where the allyl ligand is tightly bound to the metal through only two carbons. A third carbon, *weakly* associated to the metal, resembles a carbocation, and is indicated as such in figures herein (Fig.2). Combining cold solutions of **2** and tetrabutylammonium borohydride generates WTp(PMe_3)(NO)(η^2-1,3-cyclohexadiene) exclusively (**4**). Despite the coexistence of the allyl conformer **3** in solution, the WTp(PMe_3)(NO)(η^2-1,4-cyclohexadiene) complex (**8**) is undetected (Fig. 2) in the reaction mixture.[16] The η^2-diene complex **4** was then treated with either DPhAT or HOTf/MeOH acids to generate the η^2-allyl complex (**6**).[16] When **6** was subjected to base, it deprotonated to form **5**, a stereoisomer of **4**,[16] in which the uncoordinated double bond is now distal to the PMe_3.[16] Combining the allyl complex **6** with a hydride source produced the desired η^2-cyclohexene complex **7** (67%). Crystals suitable for X-ray structure determinations were grown for complexes of cyclohexadiene **4**, allyl complex **6**, and cyclohexene **7**, and a rendering of these structures, along with key NOE interactions are provided in supplementary material (Fig. S4). Overlapping signals in the ^{1}H NMR spectrum of cyclohexene complex **7** precluded unambiguous stereochemical assignments of some of the ring proton signals.

By methylating the nitrosyl ligand of **7** (CH_3OTf) to generate [WTp(NOMe)(PMe_3)(η^2-C_6H_{10})]OTf, (**9**),[17] the chemical shifts of the cyclohexene ring separated to the point that each proton could be assigned with high confidence (SI sections G and H). An X-ray structure determination of **9** provided conclusive evidence for methylation of the nitrosyl oxygen (Fig. 2), analogous to earlier literature reports.[18] Strong NOE interactions between the ring endo protons and the methylated nitrosyl ligand further facilitated these assignments and quantitative NOE experiments were carried out that support the stereochemical assignments of all diastereotopic protons on the cyclohexene ring (SI, section H).

Deuterium studies

With all hydrogen resonances for the methylated η^2-cyclohexene complex **9** fully assigned, we investigated the regio- and stereochemical fidelity of the reaction sequence (Fig. 3). When the η^2-benzenium complex **11** is prepared from **1** using [$MeOD_2^+$]OTf, a loss of signal intensity is observed, corresponding to the methylene endo proton. This indicates that protonation of the η^2-benzene occurs *syn* to the metal (red, Fig. 3). A complementary experiment was next performed starting with the fully deuterated benzene complex, **17**, in which $MeOH^+$ was used as the acid source. In this case, protonation led to a single broad proton resonance for the deuterated η^2-benzenium complex **18**. This proton signal is ~ 0.03 ppm upfield from its proteo counterpart, consistent with a primary H/D isotopic shift.[19] The endo-selective protonation of the benzene ligand in **1** is in stark contrast to the addition of carbon and heteroatom electrophiles, which have been observed to add *anti* to η^2-arene and η^2-diene ligands of tungsten complexes.[9] When η^2-benzenium complexes **11** and **18** were treated with $NaBD_4$ or $NaBH_4$, respectively, the complementary cyclohexadiene complexes **12** and **19** were formed (Fig. 3). A comparison of NOESY data for all three isotopologues of the cyclohexadiene complex (**4**, **12**, **19**) confirms that the proton delivered from the borohydride reagent is anti to the metal (Fig. 3). The cyclohexadiene complexes **12** and **19** were then taken forward to their π-allyl analogs **13**, **15**, and **20** (Fig. 3). In contrast to protonation of the η^2-benzene ligand of **1**, the acidic hydrogen was delivered predominantly *anti* to the metal (Fig.3).

The resulting η^2-allyl complexes (**13**, **15**, **20**) underwent a conformational change ("allyl shift") such that the second proton added becomes H_{6exo} (conversion of **4** to **6**, Fig. 2), while the first proton added is now H_{5endo}. For allyl complexes **13** and **20**, full stereoselective protonation was achieved. However, with the preparation of **15** or **26** we experienced difficulties in achieving full deuterium incorporation, owing to an unusually large DKIE (k_H/k_D ~37 at −30 °C for the deuteration of **12** or **4**). This DKIE was determined for **4** as the average value from three separate experiments in which **26** was generated from acidic solutions with differing H/D ratios (SI, section K). This DKIE could be decreased by raising the temperature to 22 °C, however such action compromised the stereofidelity of the resulting deuterated product (**15**), with endo deuteration of the η^2-diene **12** now competing with exo deuteration. Consequently, stereoselective deuterium incorporation at the H_{6exo} position of cyclohexene (i.e., **16**, **33**-**35**, **41**, **44**, **49**, **51**; Fig. 3) could not be achieved above ~75–80%. A similar outcome was observed when we tried to convert the d_6-isotopologue, diene **19** to allyl **30**. Finally, as before, treatment of **13**, **15**, or **20** with a hydride or deuteride

source confirmed that the corresponding η^2-cyclohexene products (**14**, **16**, **21**) are formed by nucleophilic addition *anti* to the metal (Fig. 3). Similar to the 1,3-diene complex **4**, its isomer **5** undergoes exo protonation to form the allyl complex **24**. Remarkably, treatment of the 1,4-cyclohexadiene complex (**8**) with D^+ ($D_2NPh_2^+$ in MeOD) also undergoes direct exo protonation (Fig. 3), this time providing allyl **25**. The direct exogenous protonation of the *unconjugated* C=C bond in **8** appears to result in a carbocation that DFT calculations reveal can be stabilized by the participation of the nitrosyl ligand. A subsequent [1,2]-hydride shift results in the formation of the allyl complex **25** (Fig. S5). Unambiguous assignment of the deuterated hydrogen atom in **25** comes from its conversion to **9-*d*$_1$** (via **39**; Fig. 3). In order to demonstrate regio- and stereocontrol of deuterium incorporation, additional deuterated isotopomers of the allyl complex were prepared from the monodeuterated dienes **22** and **23**, and from the benzene-d_6-derived allyls **30** and **31**(Fig. 3). The allyl complexes **24**-**31** were then combined with deuteride or hydride to form 18 additional cyclohexene complexes **32**-**46**, **49**-**51**. In principle, one can *selectively* make 10 different isotopologues of the cyclohexene complex using the procedures outlined above (d_0-d_4; d_6-d_{10}), eight of which (**7**, **16**, **32**-**38**) are reported herein.

Levels of isotopic purity for the cyclohexene ligand isotopologues were determined by recording HRMS data for the corresponding complexes as their methylated adducts (Fig. 2. **9**-d_n), in order to create a suitable cation for ESI mass analysis. Using the isotope envelope of **9**-d_0 as a reference (Fig. S6), the isotopic purity of **7**, **16**, and **32**-**38** (as converted to **9**-d_n) was estimated to be >90%, with the exception of **16** (79%), for which the high DKIE of the second protonation prevented complete deuteration at the H_{6exo} position (vide supra). Finally, as a demonstration of how the {WTp(NO)(PMe_3)} system precisely governs both the stereochemistry and regiochemistry of protonation and hydride addition, a series of five monodeuterated (**32**, **39**-**42**), seven dideuterated (**14**, **33**, **35**, **43**-**46**), and four trideuterated (**34**, **49**-**51**) isotopomers of the cyclohexene complex were prepared from these methods (Fig. 3).

Oxidation of the tungsten complex **7** with DDQ releases the free cyclohexene (Fig. 2; **10**). Such action on **32**, **42**, **45**, and **46** confirmed the expected regiochemistry of these d_1 and d_2 isotopomers of cyclohexene via ^{13}C NMR. Introduction of a single deuterium in 3-deuterocyclohexene or 4-deuterocyclohexene allows one to distinguish all six of the carbons in the ^{13}C NMR spectrum, owing to isotopic shifting of the now asymmetric cyclohexene carbons (Fig. S7). Alternatively, solvent-free heating of various isotopologues of the methylated complex **9** effected the release of the cyclohexene ligand for analysis by MRR spectroscopy (SI, section L).[20] These experiments determined that 1) over-deuteration is exceedingly low (< 2%). 2) the stereoselectivity is excellent when assessed by observation of undesired cis/trans isomers, which in the worst case is 22:1 and in other cases it is 40:1 or higher. 3) The dominant stereoisotopomers in all cases are those predicted by ^1H NMR data. As a final check of stereochemical assignments, the locations of the deuterium atoms were confirmed for complex **45** by neutron diffraction (SI section I; TOPAZ at ONRL).

Mechanistic considerations

The reaction of **1** with D^+ to form **11** results in deuterium incorporation exclusively endo to the metal, but this does not definitively show which carbon is initially protonated (Fig. S8). Given that the endo proton of the benzene ligand in **1** completely preempts protonation from an exogenous acid (exo), we propose that the protonation must be concerted - that *C-H bond formation is intramolecular and simultaneous with electronic changes at the metal* - which could lower the activation barrier for this process relative to protonation by an external acid. Such a mechanism could occur via a hydride intermediate, but this seems sterically untenable. Rather, we propose a mechanism (SI section M) in which the nitrosyl ligand first is protonated to form a hydroxylimido ligand analogous to that reported by Legzdins et al.[21] This action is followed by a concerted proton transfer in which a gamma carbon of the benzene is protonated simultaneously with release of electron density back into the tungsten through the NO group. The role of nitrosyl ligands in intramolecular proton transfer has been previously documented.[22] In contrast, the stereochemistry and kinetics of η^2-diene protonation (e.g., **4**, Fig. 2) indicates the hydrogen is delivered exogenously, anti to the tungsten (Fig 1). We speculate that while endo protonation may still be accessible for these 1,3-cyclohexadiene complexes, the less-delocalized diene ligand is most likely more basic than its η^2-benzene predecessor, and its direct exo protonation apparently preempts the purported endo mechanism at −30 °C.

Transition metal promoted protonation of benzene was observed in the η^4-benzene complexes $Cr(CO)_3(\eta^4\text{-benzene})^-$ and $Mn(CO)_3(\eta^4\text{-benzene})^-$ by Cooper et al,[23–24] and was proposed to occur via hydride intermediates.[23–24] More recently, Chirik et al have explored the molybdenum-catalyzed reduction of benzene and cyclohexadiene, with D_2 (g), which resulted in mixtures of isotopologues of cyclohexane.[12] However, reduction of cyclohexene with D_2 produced a single cis isotopomer of 1,2-dideuterocyclohexane using the molybdenum catalyst.

The high stereoselectivity enabled by the tungsten system provides unprecedented control over the preparation of specific isotopologues and isotopomers of cyclohexene, starting from either benzene complex **1** or its deuterated analog **17**, and utilizing either proteated or deuterated sources of acids and hydrides (Table S1). As illustration, consider the d_2 isotopologue of the cyclohexene complex, **7**-*d*$_2$. Given that the {WTp(NO)(PMe_3)} system is available in enantioenriched form,[15] one has access to 14 different isotopomers (individual enantiomers of **14**, **33**, **35**, **43**-**46**; Table S2). The cyclohexene-*d*$_2$ ligand of these complexes, once removed from the metal by oxidative decomplexation, would be available as 11 individual isotopomers: both enantiomers of *cis-3,4-*, *trans-3,4-*, *cis-3,5-*, *trans-3,5-*, *trans-4,5-*, and the meso compound *cis-3,6-*dideuterocycloohexene. Similarly, 11 distinct isotopomers of cyclohexene-*d*$_8$ should be available from this methodology starting from benzene-*d*$_6$. Regarding cyclohexene complex **7**-*d*$_3$ and **7**-*d*$_7$, 8 isotopomers of each would be available, and all 16 of these complexes would yield a unique, chiral cyclohexene (8 cyclohexene-*d*$_3$, and 8 cyclohexene-*d*$_7$). All totaled, (Table S2) the methodology outlined herein could provide access to 52 unique isotopomers of cyclohexene, as derived from benzene and benzene-*d*$_6$. For reference, the total number of isotopomers for cyclohexene is 528.

The ability of {WTp(NO)(PMe_3)}to be optically resolved on a practical scale and to retain its stereochemical configuration, even when undergoing ligand displacement,[15] also makes it a valuable tool for determining the isotopic pattern of cyclohexene H/D isotopomers produced by other methods.[8] Consider for example a scenario in which an unknown isotopomer of cyclohexene-d_1 is combined with the resolved form of benzene complex *(R)*-**1** in solution and allowed to undergo ligand exchange. Even though the two faces of the cyclohexene ring will bind to tungsten with equal probability, the ^{1}H NMR spectrum will be unique for each of the five possible isotopomers (SI section C; Fig. S11). A similar approach could be taken for any cyclic alkene (e.g., dehydropiperidines, pyrrolines, cyclopentenes) for which an ^{1}H NMR spectrum of a fully proteated species can be fully assigned (vide supra).

Deuterated building blocks for medchem

The development of deutetrabenazine, is considered by many as a prelude to a new generation of medicines and therapies that incorporate deuterium into the active pharmaceutical ingredient.[5] Given that *each stereoisotopomer of a biologically active substance will have its own unique pharmacokinetic profile*, the ability to stereoselectively deuterate cyclohexene or other medchem building blocks could enable the development of new probes, fragment libraries, and leads for medicinal chemists, as well as providing a new tool for organic and organometallic mechanistic studies. Cyclohexene can be readily converted into perhydroindoles,[25] perhydroisoquinolines,[26] and azepines.[27] However, the inability to chemically differentiate the two alkene carbons or the enantioface of the deuterated cyclohexene limits its potential. But by replacing the benzene ligand in Fig. 2 with a substituted benzene, or utilizing a non-hydrogenic nucleophile in the conversion of **6** to **7** (Fig. 2), one can envision a series of 3-substituted cyclohexenes with highly defined isotopic patterns. As proof of concept, we prepared the α,α,α-trifluorotoluene complex WTp(NO)(PMe_3)(η^2-CF_3Ph),[28] which can be elaborated into a 3-(trifluoromethyl)cyclohexene complex (**47**) analogous to the cyclohexene complex **7** (Fig. S14). Liberation of the cyclohexene from {WTp(NO)(PMe_3)} can be accomplished by a one-electron oxidant such as DDQ, Fe(III), or $NOPF_6$ in yields ranging from 70–75%.[28] Oxidation of **47** would generate a cyclohexene that has been previously shown to undergo diastereoselective epoxidation, and would therefore be an attractive building block for medicinal chemistry.[29] Repeating the synthesis of **47** with deuteride in the final step yields the *cis*-6-deutero-3-(trifluoromethyl)cyclohexene complex **52** in 95% yield. Various other isotopologues of **47** and **52** were also prepared (**47**, **52**, **53**, **54**), and the reaction pattern was found to be similar to that observed for benzene. Prepared compounds are summarized in Fig. 4, with synthetic details provided in SI section B. Notably, in the syntheses of **47**, **52**, **53**, **54**, protonation at the carbon bearing the CF_3 group ultimately occurs endo to the metal, allowing the CF_3 group to assume an exo stereochemistry. However, if the purported diene intermediate is protonated under kinetic control, exo protonation forces the CF_3 group endo, and the result after a second hydride reduction is the cyclohexene complex **55**. Exploiting this reactivity feature, we were able to prepare other isotopologues of **55** with inversion of the stereocenter bearing the -CF_3 substituent (Fig. 4, **56**, **57**; Fig. S14).

As further demonstration of the ability of this methodology to selectively prepare isotopomers of functionalized cyclohexenes, we have prepared the tungsten complex of *cis,trans*-3-cyano-4,5-dideuterocyclohexene (**58**) by the addition of cyanide to the allyl intermediate **13** (57%; dr > 98%; Fig 4.). Other d_1-isotopolouges were also prepared (Fig. S15) and the stereochemistry could again be controlled with the sequence of nucleophiles. For example, **58**, **59** and **60** could be prepared by generating the appropriate isotopologue of the tungsten-allyl complex and then treating with NaCN (Fig. S16). Conversely, treating the benzenium **2** with NaCN leads to a cyano-substituted cyclohexadiene that can be subsequently combined with acid and hydride source to generate other cyclohexene isotopomers (**61–63**; SI section B). 3-cyanocyclohexene (proteo form) has been previously used as a precursor to cytotoxic mustards that are of interest in cancer research.[30] Allyl-substituted cyclohexenes theoretically exist as 1024 different H/D isotopomers (512 for each enantiomer). Using the tungsten dearomatization methodology, the CF_3- and CN-substituted cyclohexenes are accessible as 64 and 60 unique isotopomers respectively. We further note that a full range of both carbon and nitrogen nucleophiles has now been demonstrated to add to tungsten benzenium and allyl tungsten complexes,[31] which demonstrates the broad scope of compounds that can now be prepared as various deuteroisotopomers.

Data Availability

All data is available in the main text or the supplementary materials, including NMR spectra, experimental details, crystallographic information, DFT calculations, Rotational spectroscopy, and HRMS data. CCDC 1885723–1885725 and 1972890 contains the supplementary crystallographic data for this paper (**4**, **7**, **9** [X-ray] and **45** [neutron]). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The authors acknowledge the assistance of Dr. Earl Ashcraft in collecting HRMS data.

Funding: National Institutes of Health (1R01GM132205-01); University of Virginia. Single crystal neutron diffraction experiment performed on TOPAZ used resources at the Spallation Neutron Source, a DOE Office of Science User Facility operated by the Oak Ridge National Laboratory, under Contract No. DE-AC05-00OR22725 with UT-Battelle, LLC.

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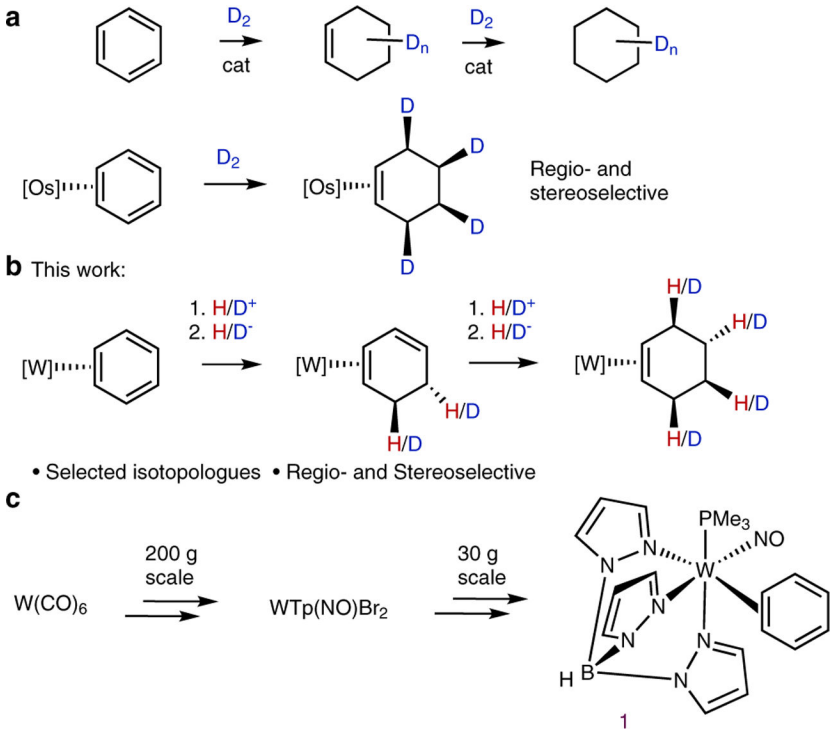

Fig. 1. Methods for the deuteration of benzene:

a), Prior methods for the selective deuteration of benzene can lead to over-reduction and a mixture of isotopologues. **b)** The current approach provides access to cyclohexene isotopologues and stereoisotopomers, **c)** the dearomatized benzene complex WTp(NO)(PMe_3)(η^2-benzene).

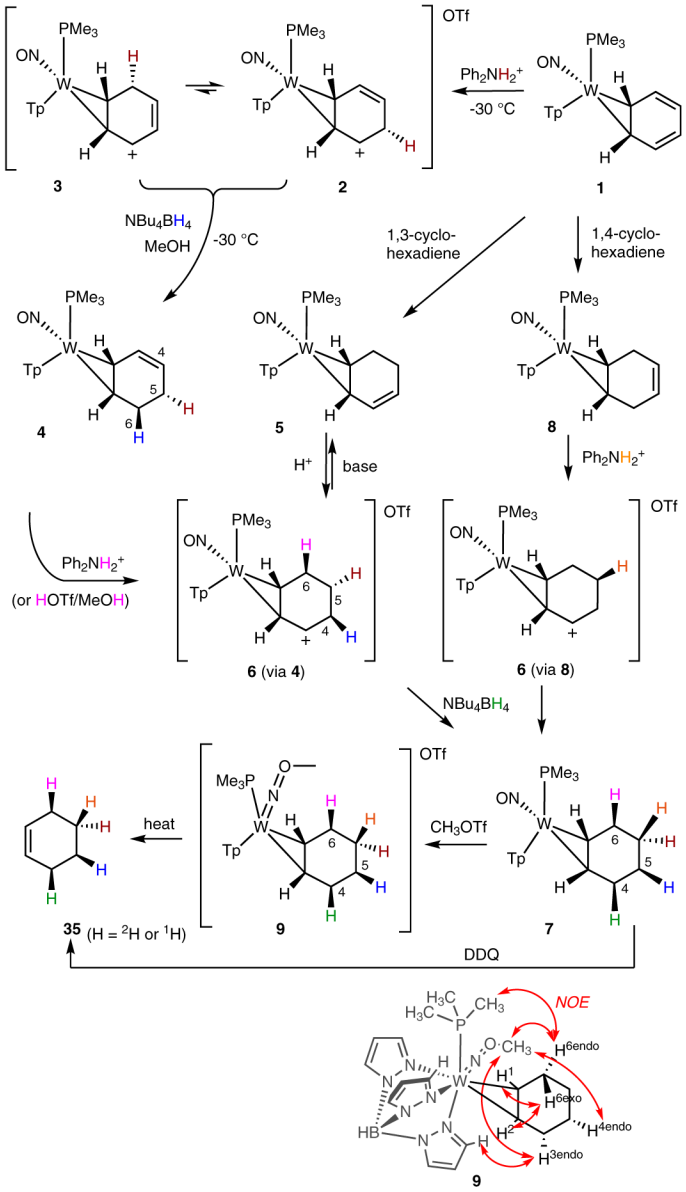

Fig. 2. Formation of tungsten-bound cyclohexene from benzene:

a)The sequential reduction of benzene to cyclohexene bound to tungsten (by addition of ^{1}H or ^{2}H). **35** confirmed by 13C-NMR and rotational spectroscopy, **9** confirmed by quantitative NOE, **b)** Crystal structure and relevant NOE interactions (red arrows) for methylated cyclohexene complex **9** ($Ph_2NH_2^+$ as OTf salt).

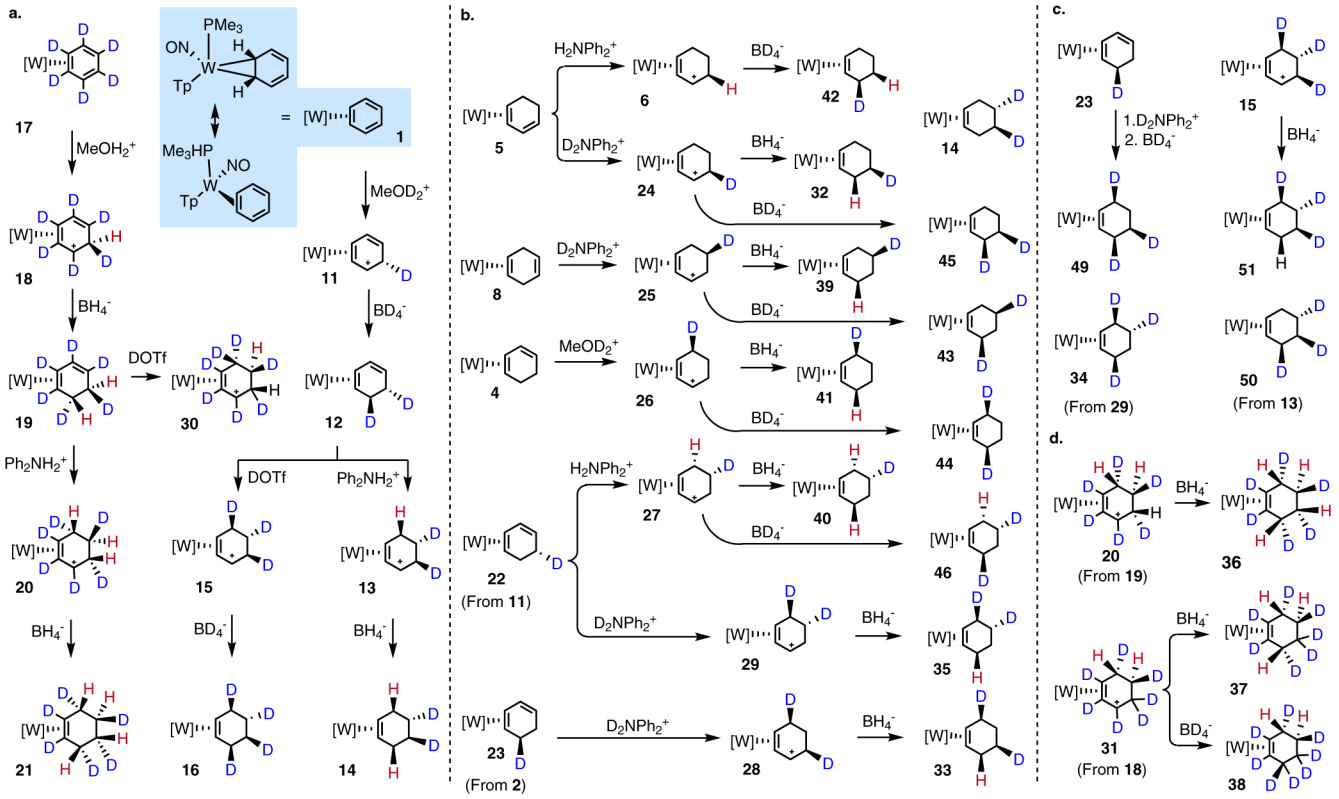

Fig. 3. Synthesis of isotopologues and stereoisotopomers of the cyclohexene complex 7.

a) detailed syntheses of d2, d4, and d6 isotopologues b) synthesis of d1 and d2 isotopologues c) synthesis of d3 isotopologues d) synthesis of d6, d7, and d8 isotopologues.

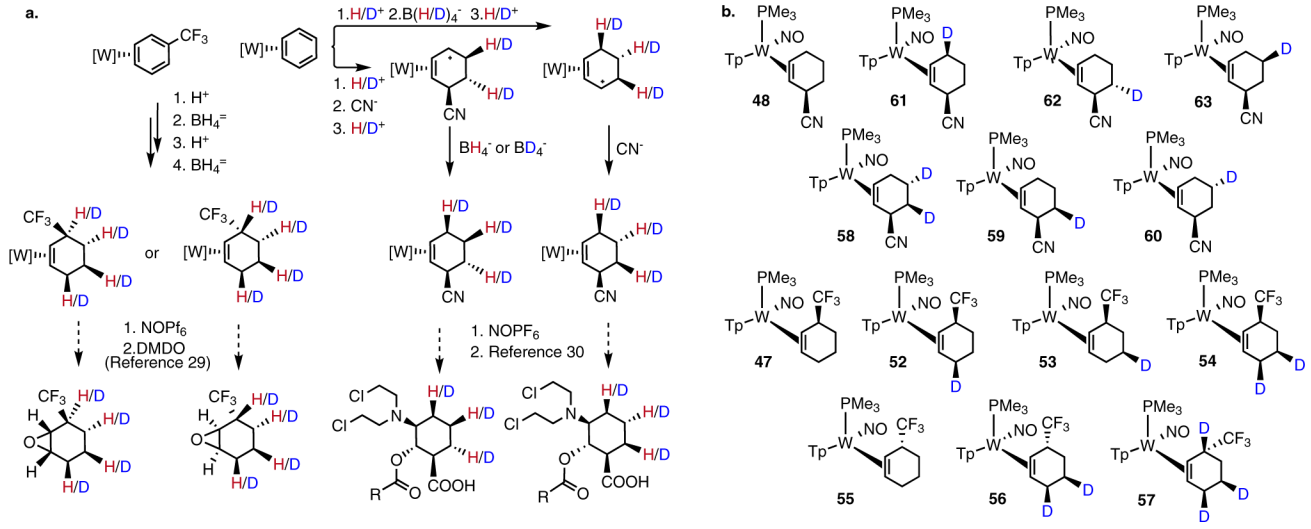

Fig. 4. Examples of functionalized cyclohexene isotopomer complexes.

a) elaboration (speculated) of functionalized cyclohexenes; reference 29 (Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M.,Diastereoselectivity in the Epoxidation of Substituted Cyclohexenes by Dimethyldioxirane J. Org Chem. 1996, 61, 1830–1841) describes a single step reaction with DMDO (70%); reference 30 (Leiris, S.; Lucas, M.; Dupuy d'Angeac, A.; Morère, A., Synthesis and biological evaluation of cyclic nitrogen mustards based on carnitine framework. European Journal of Medicinal Chemistry 2010, 45, 4140–4148) describes a 9-step synthesis that includes: i) HCl/H_2O. ii) isobutylene. iii) mCPBA. iv) NaN_3. v) acetyl chloride. vi) H_2/C. vii) ethylene oxide. viii) TsCl. ix) TFA. **b**) See SI section B for full synthetic details of **47**, **48**, **52-63**.