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Mechanistic Aspects of the Palladium-Catalyzed Isomerization of Allenic Sulfones to 1-Arylsulfonyl 1,3-Dienes

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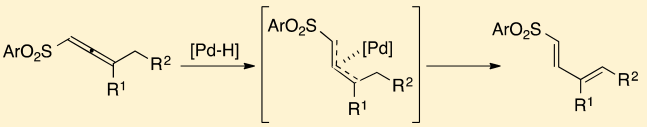
Supporting Information

ABSTRACT: When an allenic sulfone is treated under palladium catalysis in the presence of a weak acid, isomerization to a 1-arylsulfonyl 1,3-diene occurs. Investigations of the mechanistic aspects of this isomerization were performed, leading to the mechanism proposed herein. Some further studies of reaction parameters are reported.

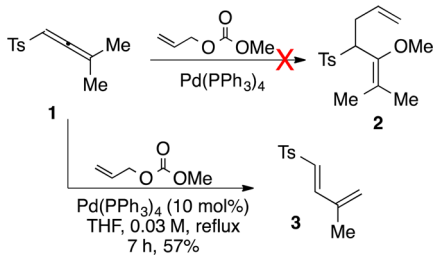


INTRODUCTION

A group of compounds known as allenic sulfones are very versatile in organic synthesis[1] as a result of their ability to participate in many different types of reactions, including cycloaddition and cyclization reactions.[2] An advantage of using an allenic sulfone in comparison to other allenic derivatives is that the sulfone moiety can be used as a handle to control the chemistry desired and can be easily removed or modified once it has served its purpose or can be used as a building block for other chemistries.[3] The electron-withdrawing nature of the sulfone group adjacent to the π-system and its ability to stabilize an α-carbanion allows the α,β-unsaturated sulfone that is part and parcel of an allenic sulfone to undergo conjugate addition at the β-carbon.

As an application of allenic sulfone chemistry in our group,[4] we were interested in generating an alkoxyallylic sulfone of the type **2** via the process shown in Scheme 1. In this process, the

Scheme 1. Attempted Alkoxyalkylation of an Allenic Sulfone

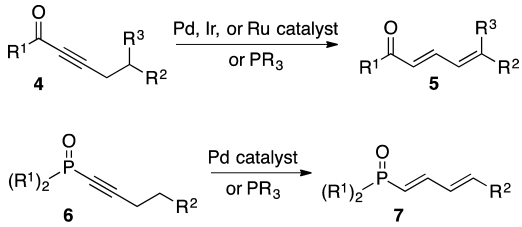


reaction of **1** in the presence of tetrakis(triphenylphosphine)-palladium(0) led to an isomerization of the allenic sulfone to the 1-arylsulfonyl-1,3-diene **3**. We recently reported the initial discovery of this reaction.[4a]

In 1988, the isomerization of acetylenic alkynones to conjugated (*E,E*)-dienones was reported by the Trost group employing palladium catalysis and by the Lu group using ruthenium catalysis.[5] Soon after, Inoue and Imaizumi reported another ruthenium catalyst that was effective at catalyzing this reaction.[6] Further study by Lu showed that $IrH_5[P(iPr)_3]_2$ was also an efficient catalyst.[7] Each group proposed allenyl intermediates as part of the mechanism that were similar to those reported by Suzuki and Morooka in the isomerization of acetylenic silyl ethers to dienol silyl ethers by ruthenium hydride complexes.[8]

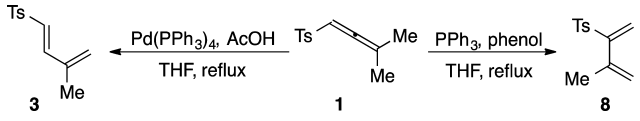
In the mid-1990s, the isomerization of acetylenic phosphorus compounds was also reported to occur in a manner similar to that of carbonyl compounds.[9] Later studies of both acetylenic carbonyl[10] and phosphorus compounds[11] showed that the reaction was able to proceed under only phosphine catalysis (Scheme 2).

Scheme 2. Isomerization of Acetylenic Carbonyl and Phosphorus Compounds



When simple phosphine catalysis is applied to allenic sulfones, a regioisomeric 2-substituted diene is produced (Scheme 3);

Scheme 3. Regiodivergent Reactions of Allenic Sulfones



the mechanistic studies of this phosphine-catalyzed reaction were recently reported.[4b] This comes as a result of the "chameleon" nature of the sulfone group, which can behave as either an

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anionic stabilizing group or a leaving group.[3b,d,6,7,12] Therefore, to enable isomerization of the allenic sulfones to occur in a manner similar to that of the carbonyl and phosphorus compounds, a mechanism that does not involve the expulsion of a sulfinate group must be employed; this is where palladium comes into play. For the formation of 1-arylsulfonyl dienes, we proposed a mechanism that involves palladium hydride chemistry to induce the double-bond isomerization of the allenes. Herein we detail the results of our study of the mechanism of this isomerization and some further examination of reaction parameters.

RESULTS AND DISCUSSION

Examination of Reaction Parameters. As previously described,[4a] the best catalyst system found for the isomerization of allenic sulfones to 1-arylsulfonyl-1,3-dienes was a mixture of tetrakis(triphenylphosphine)palladium(0) (10 mol %) and acetic acid (10 mol %). The scope of this reaction was examined with several allenic sulfones, whose dienyl products along with their yields are shown in Figure 1.

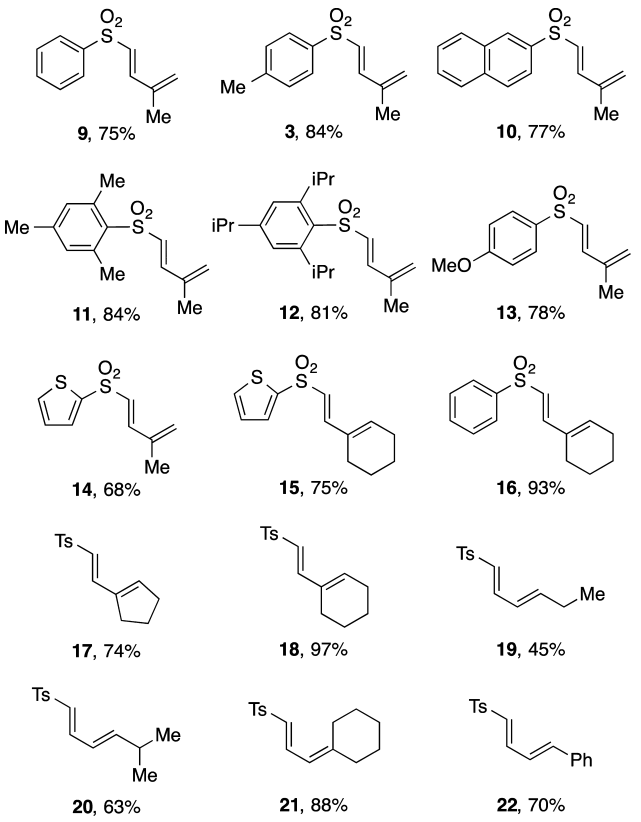

Figure 1. 1-Arylsulfonyl 1,3-dienes prepared via isomerization by palladium catalysis.

It was seen in our previous report[4a] that, as the aryl ring of the sulfone became more electron-deficient, the 1-substituted dienes were not the only products obtained. Instead, increasing or complete formation of the regioisomeric 2-arylsulfonyl-1,3-dienes was observed. In the case of the dimethyl-substituted allenes **23** and **24**, the reaction afforded only the 2-substituted dienes **27** and **29** in 56% and 61% yields, respectively (Table 1, entries 4 and 6). Additionally, with allene **25**, the reaction afforded a 54% yield of an inseparable mixture of the expected product **30** as well as the corresponding 2-arylsulfonyl 1,3-diene **31** in a 1:4 ratio (Table 1, entry 8). These outcomes are the result of the nucleophilic reaction with triphenylphosphine taking precedence due to the increased electrophilicity of the allene induced by the presence of an increasingly electron withdrawing sulfone. The triphenylphosphine required for this transformation to occur is liberated from $Pd(PPh_3)_4$ in solution,[13] and the nucleophilic attack on the allene proceeds more quickly than the Pd-catalyzed process, leading to formation of the 2-arylsulfonyl dienes. On the basis of our proposed mechanism of the formation for the 2-sulfonyldienes,[4a] we sought to correct this problem by modifying the reaction conditions to circumvent the nucleophilic process and allow formation of the 1-arylsulfonyl-1,3-dienes. Since phosphine nucleophilicity is based on both electronic and steric effects,[14] we anticipated that a phosphine ligand with a cone angle larger than that of triphenylphosphine would perform appropriately. It was shown in our study of the phosphine-catalyzed reaction that a reaction did not proceed in the presence of sterically hindered phosphines such as tricyclohexylphosphine and tris(*o*-tolyl)-phosphine.[4b] Therefore, we chose to use tricyclohexylphosphine in the reaction, as its cone angle (170°) is considerably larger than that of triphenylphosphine (145°), anticipating that the nucleophilic catalysis would be shut down in favor of the organometallic process.[15] Thus, treatment of **23** with 10 mol % of palladium acetate and 20 mol % of tricyclohexylphosphine in refluxing THF for 3 h resulted only in the formation of **26** in 53% yield. Other examples with electron-withdrawing aryl sulfones demonstrated the efficacy of this method (Table 1). In each case, the 1-substituted dienes are the only products formed under the alternative reaction conditions (condition A), whereas the previous results with $Pd(PPh_3)_4$ gave the 2-substituted dienes or mixtures of dienes (condition B). As we had previously shown that the isomerization could be executed in the presence of $Pd(OAc)_2/PPh_3$ as the catalyst system,[4a] it is worth noting that when **24** was treated with palladium acetate and triphenylphosphine under the same reaction conditions, **29** was formed in 63% yield (Scheme 4). This demonstrates that ligand selection is important in directing the outcome of the rearrangement reaction of certain allenic sulfones.

After initial demonstration of the isomerization of allenic sulfones to 1-arylsulfonyl 1,3-dienes by palladium catalysis, further examination of the reaction conditions to improve both the yield and efficiency of the reaction was pursued. The results obtained previously[4a] showed in general that a combination of tetrakis(triphenylphosphine)palladium(0) and acetic acid worked well for the palladium-catalyzed reaction, and therefore, this catalyst system was used with **1** to study the reaction parameters.

An examination of different solvents was performed first, and it was shown that THF was a suitable choice, as it was the best solvent in the study, followed closely by acetonitrile and toluene (Table 2, entries 2 and 3). Dimethyl carbonate and 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) provided media in which the reaction was as rapid, but the isolated yields were lower (Table 2, entries 4 and 5). Dimethylformamide (DMF) and *tert*-butyl methyl ether (TBME) were also suitable, but not as efficient (Table 2, entries 6 and 7). Dichloromethane was unsuitable as a solvent for the isomerization, leading to a 59% recovery of the starting material and no conversion to product (Table 2, entry 8).

After determining that THF was the best solvent for this isomerization, we evaluated the effect of catalyst loading on the reaction time and yield. The catalyst loading can be lowered to 2.5 mol % with little decline in yield and relatively short reaction times (Table 3, entry 1). A concentration study to determine

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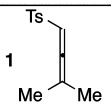
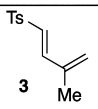
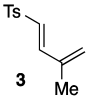
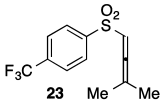
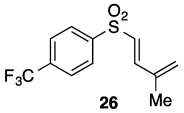
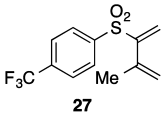
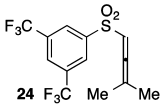
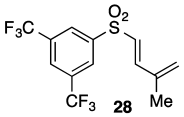
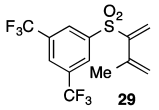
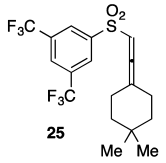
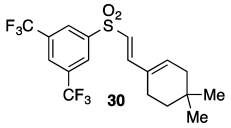
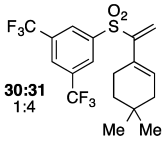
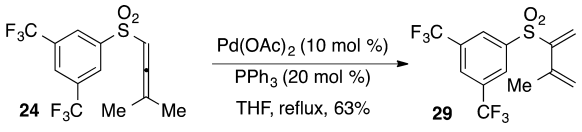
Table 1. Isomerization of Electron-Withdrawing Allenic Sulfones

Condition A: $Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%)
Condition B: $Pd(PPh_3)_4$ (10 mol%), AcOH (10 mol%)

Entry	Substrate	Condition	Time	Product	Yield (%)
1		A	2.3 h		83
2	**1**	B	20 m		84
3		A	3 h		53
4	**23**	B	20 m		56
5		A	3 h		83
6	**24**	B	25 m		61
7		A	2 h		83
8	**25**	B	40 m		54

Scheme 4. Reaction of 24 with Palladium Acetate and Triphenylphosphine



if the reaction proceeded better at higher or lower concentrations was also performed. It was found that a slightly higher yield was obtained in a more dilute reaction mixture (Table 4).

After these studies with **1**, attempts at combining some of the different reaction conditions were examined and it was found that, at a catalyst loading of 2.5 mol % and a concentration of 0.05 M in THF, the yield of **3** could be improved to 91% (Table 5, entry 2). Although the reaction required 1 h to complete, it is still a very reasonable reaction time and produced excellent results. While these reaction conditions were ideal for **1**, it is likely that an increase in yield would be observed for other allenic sulfones as well on treatment under these conditions. Therefore, a few allenic sulfones were reacted and the results are shown in Table 5. These reaction conditions were beneficial in the cases of allenes **10** and **12**; the isomerization could be completed very rapidly, accompanied by an increase in yield (Table 5, entries 4 and 6) in comparison to the previous reaction conditions (Table 5, entries 3 and 5). For diene **20**, the starting allene and product diene have identical R_f values, so ascertaining exactly when the reaction completion occurred was fallible. However, the reaction was still complete within the 2 h reaction time period and produced an almost identical yield of 65% (Table 5, entries 7 and 8). It is reasonable that there may be some variation because these conditions were optimized for a single allene example and there may be other factors that influence the reaction for other allenes.

MECHANISTIC STUDIES

Transition-metal catalysis offers a mild approach to the isomerization of alkynes to cumulated and conjugated dienes. The literature describes the use of transition-metal hydrides to perform this function. Protonation of low-valent transition

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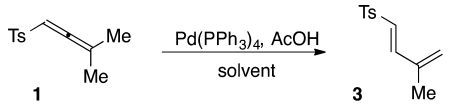
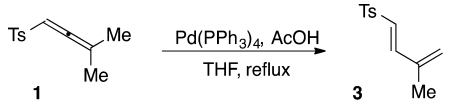
Table 2. Solvent Effects on the Palladium-Catalyzed Isomerization[a]



entry	solvent	temp (°C)	time	yield (%)
1	THF	65	20 min	84
2	toluene	80	20 min	75
3	MeCN	82	25 min	80
4	DMPU[b]	80	20 min	56
5	dimethyl carbonate	90	25 min	58
6	DMF[c]	80	1h 40 min	60
7	TBME[d]	55	8 h	80
8	CH_2Cl_2	40	25 h	[e]

[a]The reactions were conducted with 10 mol % catalyst and cocatalyst at 0.1 M concentration. [b]DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone. [c]DMF = *N*,*N*-dimethylformamide. [d]TBME = *tert*-butyl methyl ether. [e]**1** was recovered in 59% yield.

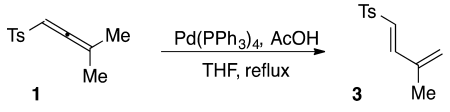
Table 3. Effects of Catalyst Loading on the Palladium-Catalyzed Isomerization[a]



entry	catalyst loading (mol %)	temp (°C)	time (min)	yield (%)
1	2.5	65	25	83
2	5.0	65	25	88
3	10.0	65	20	84

[a]The reactions were conducted at 0.1 M concentration.

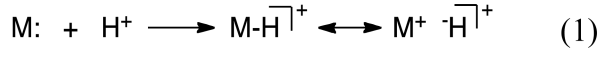
Table 4. Concentration Effects on the Palladium-Catalyzed Isomerization[a]



entry	concn (M)	temp (°C)	time (min)	yield (%)
1	0.025	65	20	88
2	0.05	65	20	81
3	0.10	65	20	84
4	0.15	65	25	86

[a]The reactions were conducted with 10 mol % catalyst and cocatalyst.

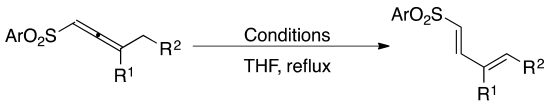
metals generates a class of reagents that contain a M−H bond. This bond may function differently from typical conjugate acids in that it may act as a hydridometal species rather than a protonated metal[16] (eq 1). As observed in many metal protonation/metal hydride complexes, umpolung of the



(1)

hydrogen occurs during the transfer of the hydrogen from an acetate as the base to the low-valent metal as the base.[16] The mechanism proposed by the Trost and Lu groups for the isomerization of alkynyl carbonyls suggested a hydridometal species, which through a series of hydrometalations/β-hydride eliminations, presumably through an allenyl intermediate, eventually led to an (*E*,*E*)-diene.[5,7,12]

Table 5. Comparison of Reaction Conditions

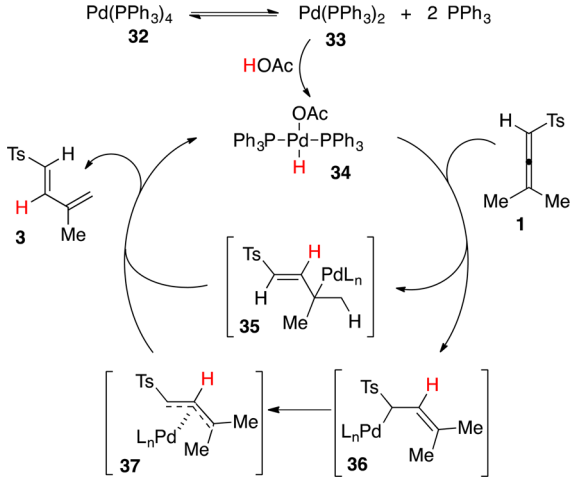


Condition A: $Pd(PPh_3)_4$ (10 mol%), AcOH (10 mol%), 0.1 M
Condition B: $Pd(PPh_3)_4$ (2.5 mol%), AcOH (2.5 mol%), 0.05 M

entry	product	conditions	time	yield (%)
1	**3**	A	20 min	84
2	**3**	B	1 h	91
3	**10**	A	45 m	77
4	**10**	B	30 m	88
5	**12**	A	3.6 h	81
6	**12**	B	30 m	84
7	**20**	A	2 h	63
8	**20**	B	2 h	65

On this basis and the data obtained initially, we proposed the mechanism shown in Scheme 5 for the metal-catalyzed isomerization of allenic sulfones to dienes. Hence, oxidative addition of a coordinatively unsaturated Pd(0) species **33** to acetic acid produces the palladium hydride intermediate **34**. This hydropalladates **1** to produce **35** or **36**. Subsequent β-hydride elimination from **35** or the π-allyl palladium intermediate **37** affords **3** and regenerates **34** (Scheme 5).

Scheme 5. Proposed Mechanism for the Palladium-Catalyzed Isomerization



Deuterium Labeling. Mechanistic insights were pursued using deuterium labeling of an allenic sulfone to demonstrate the migration of a deuterium atom via the isomerization process. This seemed reasonable on the basis of the allenic intermediates presented by others in the isomerization of acetylenic compounds.[5a,12]

It was proposed that labeling the δ carbons of an allene with deuterium and using deuterated acetic acid to form a palladium deuteride species would enable a deuterium atom to end up on the β-carbon of the diene (Scheme 6). This would result from deuteropalladation of **38** followed by β-deuteride elimination.

A few questions needed to be considered. (1) Would a combination of $Pd(PPh_3)_4$ and AcOD-d_4 generate a palladium deuteride and would this be effective in deuteropalladating an allenic sulfone? (2) Would it be possible for the α-position to be exchanged by reversible deuteropalladation/β-hydride

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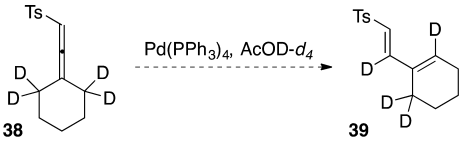
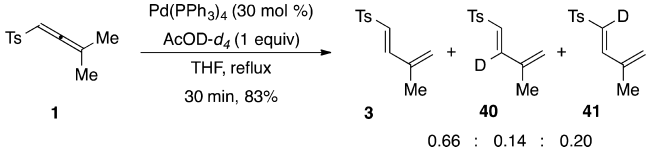
Scheme 6. Proposed Isomerization of Deuterated Allene 38



elimination? (3) Would deuterium be incorporated into a nondeuterated diene after formation by exposure to AcOH-d_4 alone or to the $Pd(PPh_3)_4$/AcOD-d_4 reaction conditions? (4) Would there be a kinetic isotope effect for the rupture of a C−D bond versus a C−H bond in this process?

First, the dimethyl-substituted allene **1** was used to examine whether a palladium deuteride could be formed and if it would deuteropalladate an allenic sulfone. The flaw with this reaction is that, in theory, there is a palladium hydride produced by β-hydride elimination for every hydro-/deuteropalladation that occurs. This, therefore, can put limits on how much deuterium can be incorporated into the product. At a minimum, this reaction would show that deuterium incorporation into the product is possible, supporting the proposal that a palladium hydride/deuteride is a key component of this reaction. Therefore, **1** was treated with a 30 mol % loading of catalyst and 1 equiv of deuterated acetic acid. After consumption of the starting material, the remaining material was purified by column chromatography. This reaction produced the protio product **3** and the β-deutero product **40**, as well as some of the α-deutero diene **41** (Scheme 7), which resulted from

Scheme 7. Incorporation of Deuterium into 1



reversible H/D exchange by deuteropalladation/β-hydride elimination.

The ratio of products formed was determined by the following:

Each signal was integrated as normal.

The doublet for the *p*-tolylsulfonyl group at 7.78 ppm was set to 2.00 protons as a reference.

The signal for the α-proton of the diene appears at 6.31 ppm. The singlet signal for the α-proton of **40** overlaps with the right half of the doublet signal for the α-proton of **3** (Figure 2).

There is no skewing of the doublet signal, and therefore, the area of the doublet can be determined to be 0.66 proton, leaving the remaining integrated area to the α-proton of **40**, which is 0.14 proton (Figure 2).

As the α-proton of **3** integrates for 0.66 proton, the β-proton of **3** will also be 0.66 proton.

The signal for the β-proton appears near 7.31 ppm, which is partially overlapped with the second signal from the *p*-tolylsulfonyl aromatic protons.

The left half of the β-proton's doublet of **3** overlaps with the aromatic signal. The right half of the β-proton's doublet of **3** overlaps with the β proton of **41** (Figure 3).

The right half of β-H of **3** should integrate to 0.33 proton, which leaves the remainder of the integrated signal at 7.30 ppm (0.20 proton) to the β-H of **41**.

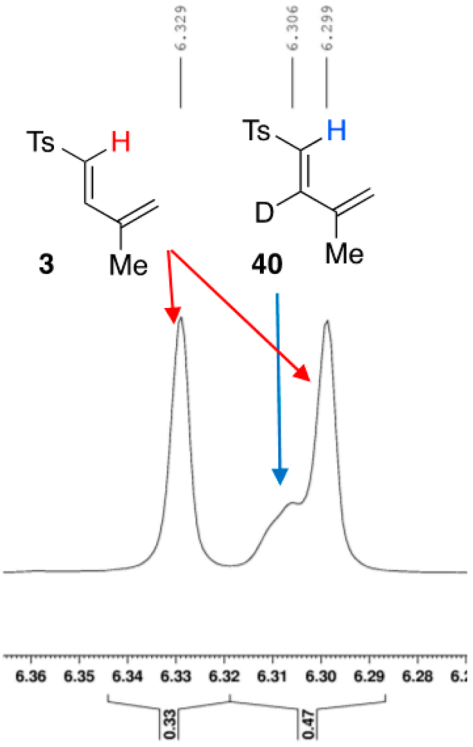


Figure 2. α-Proton signals for **3** and **40**.

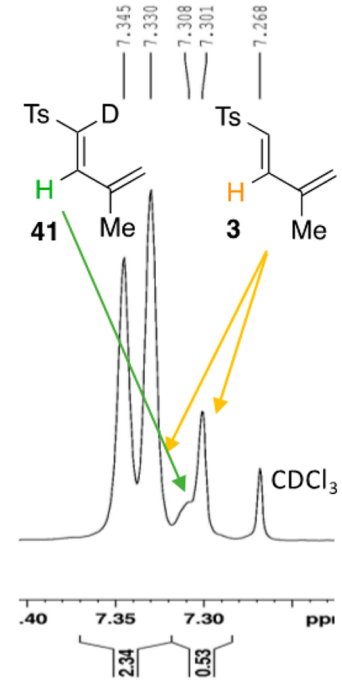


Figure 3. β-Proton signals of **3** and **41**.

Therefore, from the reaction the diene products are formed in a ratio of 0.66:0.14:0.20 for **3**:**40**:**41**.

Thus, this reaction also illustrated the ability of the α-position of the allenic sulfone to be exchanged. A faster rate of hydropalladation in comparison to deuteropalladation would explain the very small amount of deuterated products that were observed.

In 1973, Cruikshank and Davies[17] reported isotope studies of the isomerization of olefins homogeneously catalyzed by

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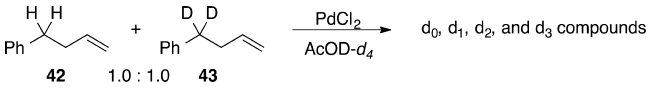
palladium and other metals. They discovered in the palladium-catalyzed reactions that the rate of disappearance of a terminal olefin was only slightly different, but the formation of the isomerized product was significantly slowed when the compound was deuterated. These data in combination illustrate an isotope effect on the breaking of a carbon−deuterium bond versus a carbon−hydrogen bond in the isomerization process. Since the disappearance of starting material is not hindered and the formation of product is slowed, this points to only the second stage of isomerization, breaking the C−D bond, as the cause. This is a clear example of a KIE for the isomerization of unsaturated bonds.

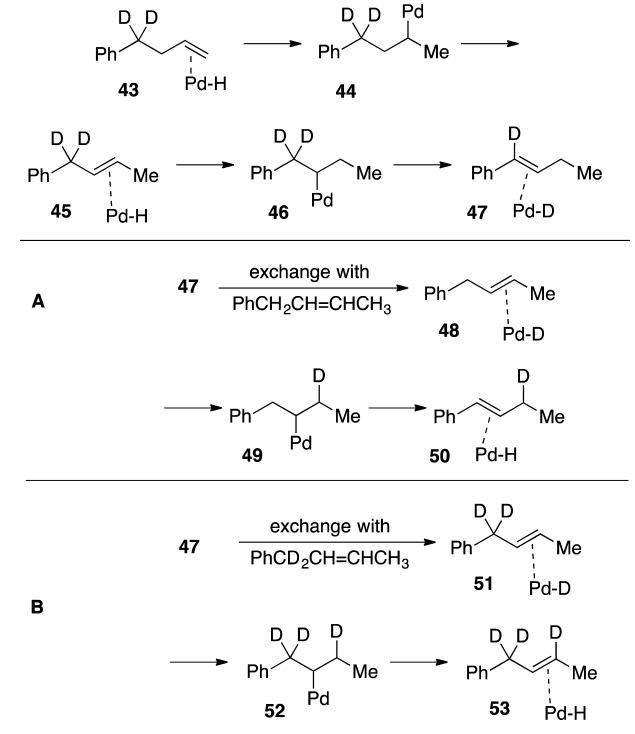
Cruikshank and Davies also noted that, when a mixture of d_0 and d_2 isotopologues were mixed and isomerized, there was formation of both d_1 and d_3 products in addition to the expected d_0 and d_2 products (Scheme 8).

Scheme 8. Deuterium Transfer between Alkenes[17a]



This indicates that a deuterium from a d_2 deuterated alkene has been transferred to a d_0 molecule to generate the d_1 species or to another d_2 molecule to generate the d_3 species (Scheme 9).[17a]

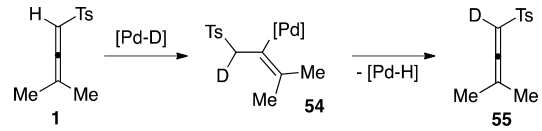
Scheme 9. Mechanism for Deuterium Transfer between Alkenes[17a]



It is by a method similar to this that the α-hydrogen of the allenic sulfone can be exchanged for a deuterium atom (Scheme 10).

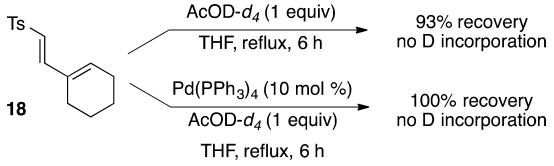
It was also necessary to confirm that any deuterium incorporated into the product diene was a result of deuteropalladation of the allene and not an insertion of deuterium after the product had already been formed. To that end, the nondeuterated diene **18** was treated with 1 equiv of deuterated acetic acid at reflux for 6 h and there was no incorporation of deuterium into the diene observed.

Scheme 10. α-Proton Exchange of an Allenic Sulfone



Then, **18** was subjected to a mixture of $Pd(PPh_3)_4$ and AcOD-d_4 at reflux for 6 h (Scheme 11). There was also no incorporation of

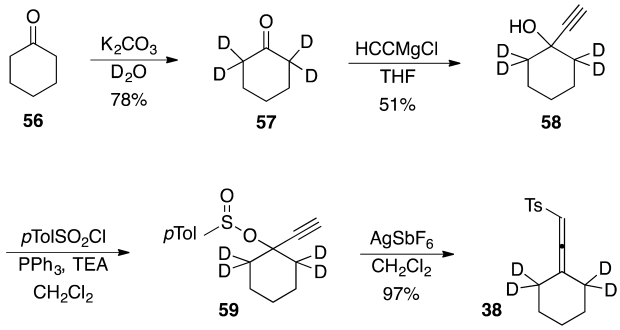
Scheme 11. Subjection of 18 to Deuterium Conditions



deuterium in this case, suggesting that deuteropalladation only occurs in the allene starting materials and not in the product dienes.

In order to examine the isomerization proposed in Scheme 6, we prepared allene **38** by the steps outlined in Scheme 12.

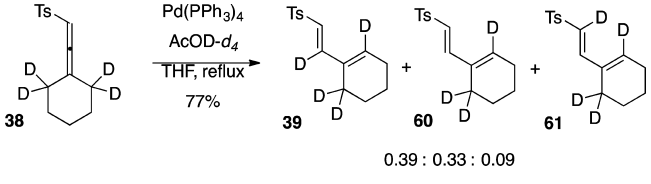
Scheme 12. Preparation of the Tetradeuterated Allene 38



Cyclohexanone was refluxed with potassium carbonate and deuterium oxide twice for 24 h for α-exchange of the protons with deuteriums. The labeled cyclohexanone **57** was then treated with ethynylmagnesium chloride in THF at −78 °C to afford the propargyl alcohol **58** in 51% yield. The sulfinate ester **59** was prepared by treating *p*-toluenesulfonyl chloride and triethylamine with a mixture of **58** and triphenylphosphine in dichloromethane.[18] This ester then underwent a [2,3]-sigmatropic rearrangement in the presence of silver hexafluoroantimonate[18] to produce **38** in 97% yield.

After some experimentation with the deuterated allene **38** with AcOD-d_4 and palladium(0) in small-scale reactions where an abundance of protons was observed in positions expected to be deuterated, we reasoned that adventitious water may be having an effect on the reaction and, therefore, further experiments were performed with glassware that had been refluxed with D_2O and then dried overnight at 110 °C. When **38** was reacted with

Scheme 13. Isomerization of 38



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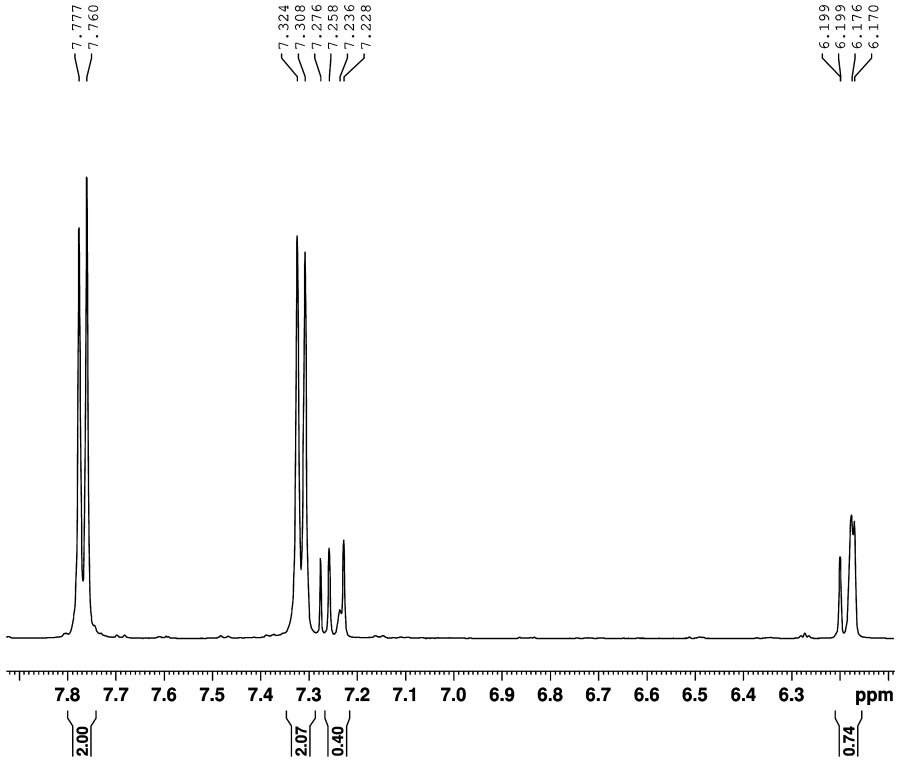

Figure 4. [1]H NMR overlapping peaks for reaction shown in Scheme 13.

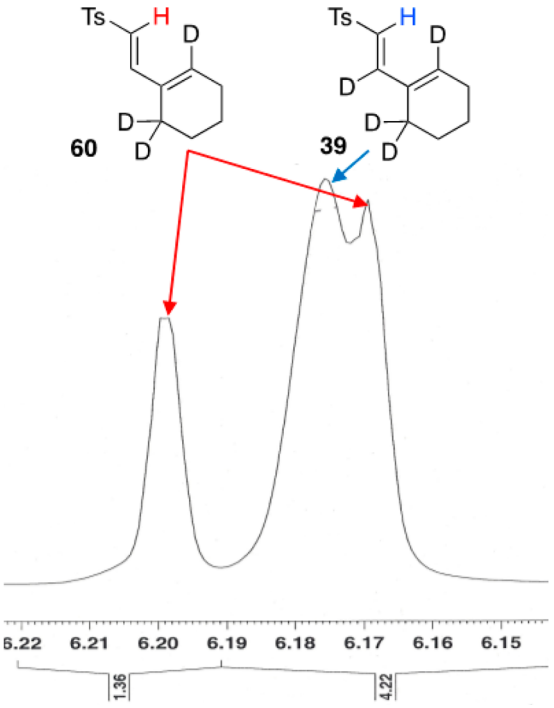

Figure 5. α-Proton signals for **39** and **60**.

$Pd(PPh_3)_4$/AcOD-d_4 (Scheme 13) in the D_2O-treated glassware, we were able to improve the ratio of deuterated diene products.

To determine the ratio of dienes in the mixture, both manual and computer-assisted integration techniques were used to determine the ratio of the dienes in the overlapping signals in the [1]H NMR (Figure 4). Using manual integration to select the area to be integrated for each signal, the following ratios were determined by an analysis similar to that discussed for Scheme 7 and Figures 2 and 3:

Each signal was integrated as normal.

The doublet for the *p*-tolylsulfonyl group at 7.77 ppm was set to 2.00 protons as a reference.

The signals for the α-protons of the diene appear at 6.18 ppm. The singlet signal for the α-proton of **39** overlapped with the right half of the doublet signal for the α-proton of **60**. This entire signal integrated for 0.74 proton.

The signals for the β-protons appear near 7.24 ppm. The singlet signal for the β-proton of **61** overlapped with the right half of the doublet signal for the β-proton of **39**. This entire signal integrated for 0.40 proton.

In a separate integration, the peaks in question were integrated in two sections each in order to determine the ratio of the compounds to one another.

For the α-proton signals, the singlet signal for **39** overlapped with the right half of the doublet signal for the α-proton of **60** (Figure 5). The area of the doublet of **60** was estimated to be 2.72 protons in comparison to the remaining integrated area for **39** equal to 2.86 protons.

For the β-proton signals, the singlet signal for **61** overlapped with the right half of the doublet signal for the β proton of **60** (Figure 6). The area of the doublet of **60** was estimated to be 2.00 protons in comparison to the remaining integrated area for **61** equal to 0.73 proton.

A summary for this method gives a ratio of

$$\alpha\text{-}\mathbf{39} = 2.86 \rightarrow = 1.43$$
$$\alpha\text{-}\mathbf{60} = 2.72 \rightarrow = 1.36$$
$$\beta\text{-}\mathbf{60} = 1.00 \rightarrow = 1.00$$
$$\beta\text{-}\mathbf{61} = 0.73 \rightarrow = 0.365$$

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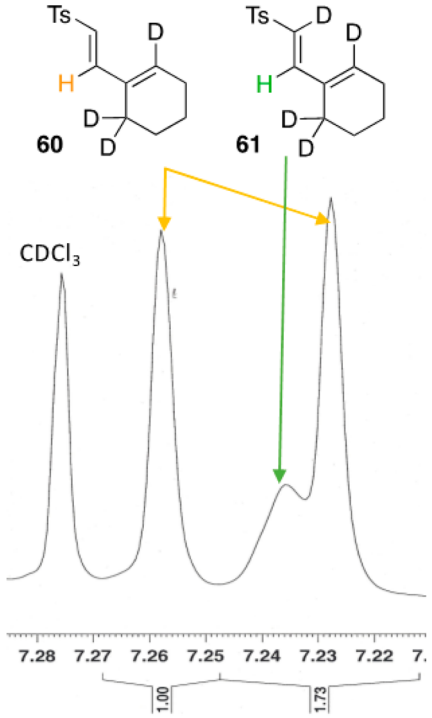


Figure 6. β-Proton signals for **60** and **61**.

The second method of integration allowed the instrument software to deconvolute the overlapping signals from one another. The integrations can be seen in Tables 6 and 7.

The total integrated area of the α-proton of **60** was 18.469 protons in comparison to the area for the α-proton of **39**, which was 22.441 protons.

The total integrated area of the β-proton of **60** was 18.327 protons in comparison to the area for the β-proton of **61**, which was 4.184 protons.

A summary for this method gives a ratio of

$$\alpha\text{-}\mathbf{39} = 22.441 \rightarrow = 1.22$$

$$\alpha\text{-}\mathbf{60} = 18.469 \rightarrow = 1.01$$

$$\beta\text{-}\mathbf{60} = 18.327 \rightarrow = 1.00$$

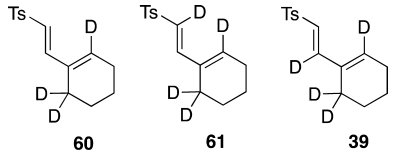
$$\beta\text{-}\mathbf{61} = 4.184 \rightarrow = 0.228$$

Next, the integrated areas on the original NMR (Figure 4) were used to calculate how much of each peak is due to each proton:

$$\frac{\beta\text{-}\mathbf{60}}{0.40} = \frac{1.0}{1.228} \rightarrow 0.326 \qquad \frac{\beta\text{-}\mathbf{61}}{0.40} = \frac{0.228}{1.228} \rightarrow 0.074$$

$$\frac{\alpha\text{-}\mathbf{60}}{0.74} = \frac{1.01}{2.23} \rightarrow 0.335 \qquad \frac{\alpha\text{-}\mathbf{39}}{0.74} = \frac{1.22}{2.23} \rightarrow 0.405$$

α-**60** and β-**60** correspond to the same molecule, and they are averaged together to approximate the ratio of compounds in the mixture (Figure 7).



60 : **61** : **39** = 0.33 : 0.07 : 0.41 = 0.81

Figure 7. Ratio of dienes determined by ^{1}H NMR integration.

The sum of the ratios of these compounds does not equal 1.0, and therefore there must be another compound that makes up the remainder of the product mixture but yet does not contribute to the vinylic hydrogens being examined. This compound is proposed to be the pentadeuterated species **62** (Figure 8).

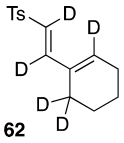


Figure 8. Pentadeuterated diene **62**.

This pentadeuterated compound **62** would be difficult to detect by ^{1}H NMR because there is no separate signal by which to identify it apart from the other diene isotopologues. The only discernible differences in the ^{1}H NMR spectra are in the vinylic region where the pentadeuterated species would not contribute; in the ^{13}C NMR, the deuterated carbon signals of **62** are the same as the other deuterated carbon signals present for **39** and **61** in the product mixture.

After showing that there was a significant amount of protons in the diene product mixture above, it was necessary to accurately determine the extent of deuteration of the starting material **38**. Initial examination of the ^{1}H NMR of **38** appeared clean with an absence of a peak where the compounds should be deuterated (by comparison to the ^{1}H NMR of the nondeuterated **7**), though integration of the same region indicated an integration of

Table 6. Computer-Assisted Analysis of the α-Proton Peaks

	frequency		width					
fit	ppm	Hz	ppm	Hz	intensity	**area**	%Lor. chisq	peak
STD:	6.199	3100.26	0.00386	1.929	0.847	**8.140**	100.00	α-**60**
STD:	6.176	3088.82	0.00772	3.860	1.167	**22.441**	100.00	α-**39**
STD:	6.169	3085.41	0.00465	2.325	0.892	**10.329**	100.00	α-**60**

Table 7. Computer-Assisted Analysis of the β-Proton Peaks

	frequency		width					
fit	ppm	Hz	ppm	Hz	intensity	**area**	%Lor. chisq	peak
STD:	7.258	3629.88	0.00404	2.023	0.897	**9.044**	100.00	β-**60**
STD:	7.236	3619.17	0.00737	3.687	0.228	**4.184**	100.00	β-**61**
STD:	7.228	3614.77	0.00386	1.932	0.964	**9.283**	100.00	β-**60**

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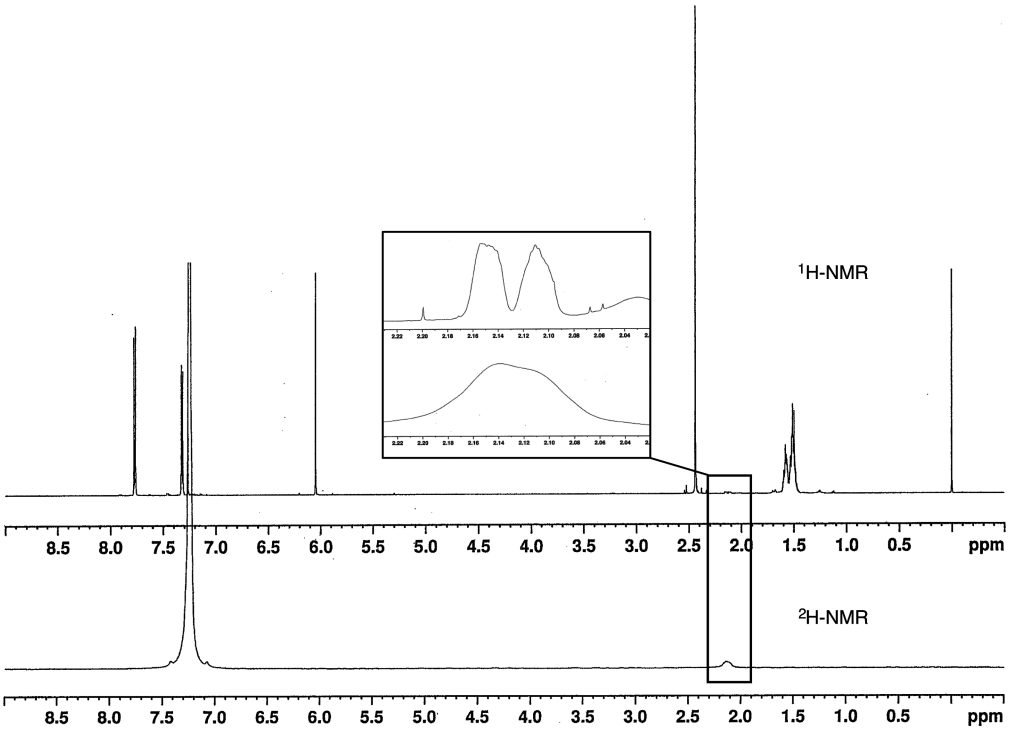

Figure 9. ^{2}H NMR vs ^{1}H NMR comparison of **38**.

~0.12 proton. ^{2}H NMR also showed this position to be the only deuterated position in the molecule (Figure 9).

To further determine the extent of deuteration of the starting allene and the ratio of diene isotopologues in the product mixture, electrospray ionization mass spectrometry (ESI-MS) was measured of both the deuterated allene **38** and the deuterated diene product mixture. It is then necessary to determine how well the experimental results aligned.

Most elements appear in nature as isotopic mixtures. These isotopes are responsible for the peaks in a mass spectrum appearing as an isotopic cluster, i.e., mass peaks that are one, two, three, etc. mass units higher than the nominal mass, due to their statistical distribution. Therefore, given the relative natural abundances of isotopes, we can calculate the theoretical relative intensities of peaks corresponding to isotopologues.[19] This comparison of ESI-MS and ^{1}H NMR data was used qualitatively to ascertain whether the isotopologue mixtures that were seen in the ^{1}H NMR of the diene product mixture corresponded with the ratios present in the starting material **38** for the reaction.

In order to calculate theoretical intensities of isotopic clusters, the relative natural abundances of isotopes that are relevant are as follows: ^{1}H, 0.99985; ^{12}C, 0.989; ^{13}C, 0.011; ^{16}O, 0.9976; ^{32}S, 0.9502; ^{33}S, 0.0075; ^{34}S, 0.0421.

The theoretical relative intensities of an isotopic cluster can be calculated by the formula shown in eq 2.

$$P(x) = (A^{1H})^{\#1H} \cdot (A)^{\#12C} \cdot (A^{13C})^{\#13C} \cdot (A^{16O})^{\#16O} \cdot (A^{32S})^{\#32S} \cdot {}_{\#13C}P_{15} \quad (2)$$

where x = mass unit, $P(x)$ = probabililty of the mass unit, A^{13C} = relative abundance of ^{13}C, etc., #13C = number of ^{13}C atoms in the molecule, etc., and ${}_{\#13C}P_{15}$ is a permutation for how many different ways there are to insert #13C atoms into the molecule.

To calculate the theoretical relative intensities of the isotopic peaks accompanying the molecular ion peak of the allenes or dienes, we consider its molecular formula of $C_{15}H_{18-n}D_nO_2S$. There are 15 carbon atoms; what is the probability of any number of carbon-13 atoms (0−15) being present in this molecule? These calculations were repeated for each isotope of sulfur (^{32}S, ^{33}S, and ^{34}S). The probabilities for each mass unit can be summed to yield a total probability. From here the percent theoretical relative abundances for an isotopic cluster can be calculated. For compounds with the formula $C_{15}H_{18-n}D_nO_2S$ (n = 2−5), the percent theoretical relative abundances are shown in Table 8.

Table 8. Theoretical Relative Abundances of Isotope Clusters

	mass	rel abundance (%)
$C_{15}H_{16}D_2O_2S$	264	100.0000
	265	17.4728
	266	7.1602
	267	1.1353
	268	0.1682
$C_{15}H_{15}D_3O_2S$	265	100.0000
	266	17.4728
	267	7.1602
	268	1.1353
	269	0.1682
$C_{15}H_{14}D_4O_2S$	266	100.0000
	267	17.4728
	268	7.1602
	269	1.1353
	270	0.1682
$C_{15}H_{13}D_5O_2S$	267	100.0000
	268	17.4753
	269	7.1746
	270	1.1377
	271	0.1686

Some of the peaks to be analyzed in the spectrum would correspond to multiple isotopologues, as demonstrated in Table 9. Given the experimental intensities of each mass peak and using the

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Table 9. Isotopologue Contributions to Mass Ion Peaks

mass peak	d_2	d_3	d_4	d_5
265	n			
266	$n+1$	n		
267	$n+2$	$n+1$	n	
268	$n+3$	$n+2$	$n+1$	n
269		$n+3$	$n+2$	$n+1$
270			$n+3$	$n+2$
271				$n+3$

theoretical isotopic cluster ratios, we can extract the final ratios of the isotopologues in the mixture.

Allene **38** was treated under isomerization conditions as shown in Scheme 14. It can clearly be seen in the ^{1}H NMR data in

Scheme 14. Diene Products from Isomerization of Allene 38

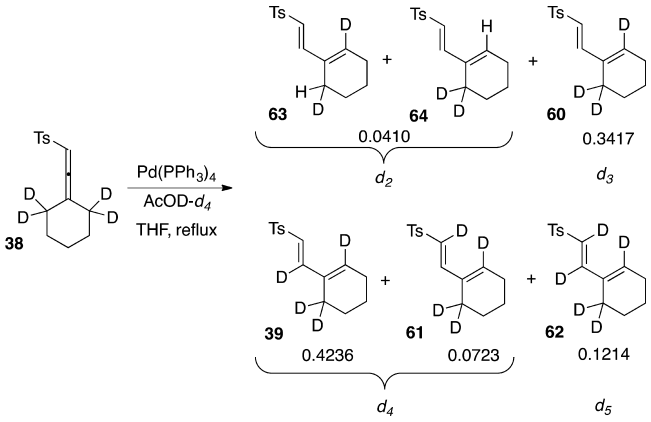

Figure 4 and the mass spectrometry data below of the product mixture that there is a mixture of isotopologues, which contains at least d_5, d_4, d_3, and d_2 compounds (Figure 10). Given the experimental peak intensities and using theoretical isotopic cluster ratios, we can extract the final ratio of the isotopologues in the mixture. After normalization, it was determined that the dienes are in a ratio of 0.0410:0.3417:0.4959:0.1214 of d_2:d_3:d_4:d_5 dienes. The two d_4 isomers can be separated by using the integration and ratio obtained by ^{1}H NMR to give a final ratio of 0.0410:0.3417:0.4236:0.0723:0.1214 of **63**/**64**:**60**:**39**:**61**:**62**.

Upon obtaining the mass spectrum of **38**, it was seen that **38** was not completely tetradeuterated. There are also peaks for lesser-deuterated compounds such as d_3 and d_2 species (Figure 11). It is necessary to determine the ratio of these isotopologues, as this may have significantly affected the composition of the product mixture of dienes. The possible isotopologues of **38** are the d_3 compound **65** and the d_2 compounds **66** and **67** (Figure 12). After normalization it was determined that the allene used in this reaction is a 0.0329:0.1362:0.8309 mixture of d_2:d_3:d_4 allenes.

Qualitatively, the mass spectrometry ratio and the ^{1}H NMR ratios (~0.12 proton in the δ-position) agree closely, and we concluded that the starting allene used in this reaction was approximately 83% tetradeuterated.

This same process was repeated on two more batches of starting material allenes and the resulting diene product mixtures. The results are consistent in that the starting allenes are generally ~82−85% tetradeuterated and the diene mixtures contain a smaller percentage of d_4 isomers, with formation of 10−20% of a d_5 diene compound. It is possible to draw mechanisms by which all of these species are generated (Schemes 15 and 16), taking

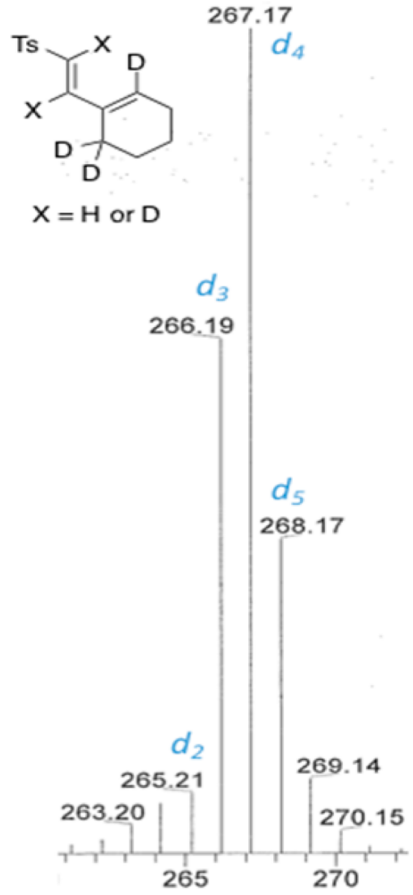

Figure 10. Mass spectrum of deuterated diene mixture.

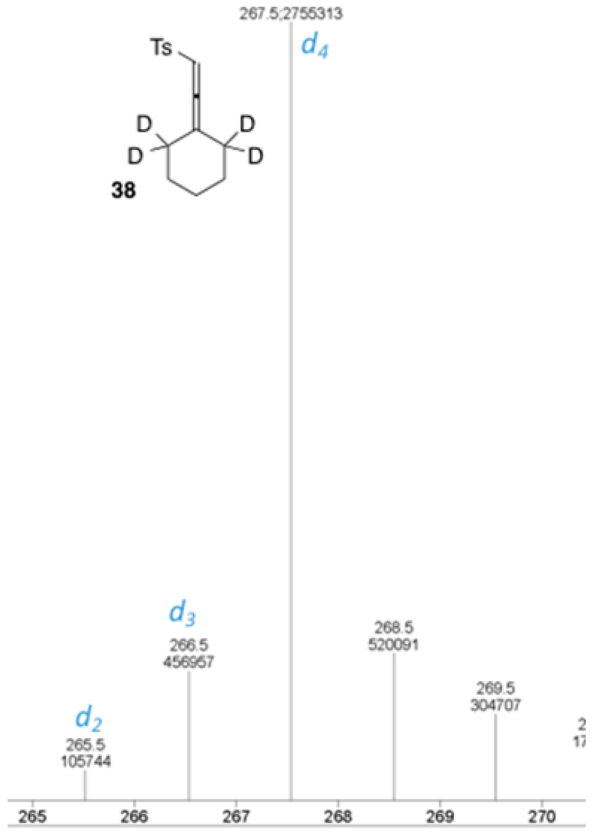

Figure 11. Mass spectrum of allene **38**.

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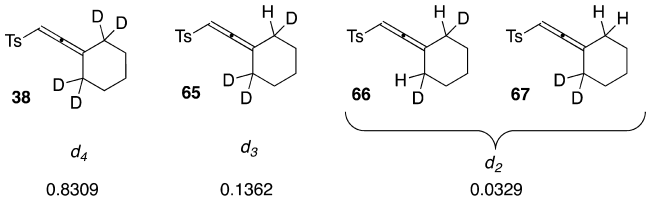


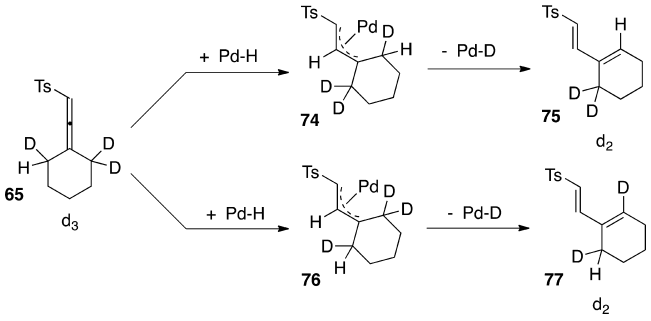
Figure 12. Isotopologues of the deuterated allene starting material.

into account that the mass spectrum shows that the allene is not fully tetradeuterated and contains some lesser-deuterated analogues.

The data above illustrate the ability of Pd–D to deuteropalladate an allenic sulfone and the fact that the α-position is interchangeable. In addition, the isotopic mixtures of diene products seen are a direct result of the extent of deuteration on the allene starting material and the redistribution of deuterium during the isomerization.

Reaction Intermediate. As a result of the formation of multiple diene products, an isomerization reaction of **38** was monitored by ^{1}H NMR to determine whether the protonated dienes were formed initially, if there was an interconversion between products, or if there were intermediates formed that were then converted to the product diene. The reaction was monitored by removing an aliquot of the reaction solution, filtering through a very small silica plug in a pipet, and evaporating the solvent at time intervals of every 30 min until reaction completion. In this reaction the formation of another *trans*-protio alkene intermediate was observed (labeled as Int = intermediate, Figure 13), which then disappears as the product dienes are formed (identified by proton signals in the ^{1}H NMR for hydrogens labeled 3 and 4 on the product diene, Figure 13). We can see during the monitoring of this reaction that both the protio and the deutero intermediates and the protio/deutero dienes are formed at the same time. As the reaction approaches completion, the ratio of the deutero dienyl product **60** increases relative to the protio diene product **39**, as there are fewer β-hydride eliminations competing with β-deuteride eliminations,

Scheme 16. Generation of d_2 Diene Isotopologues Stemming from 65

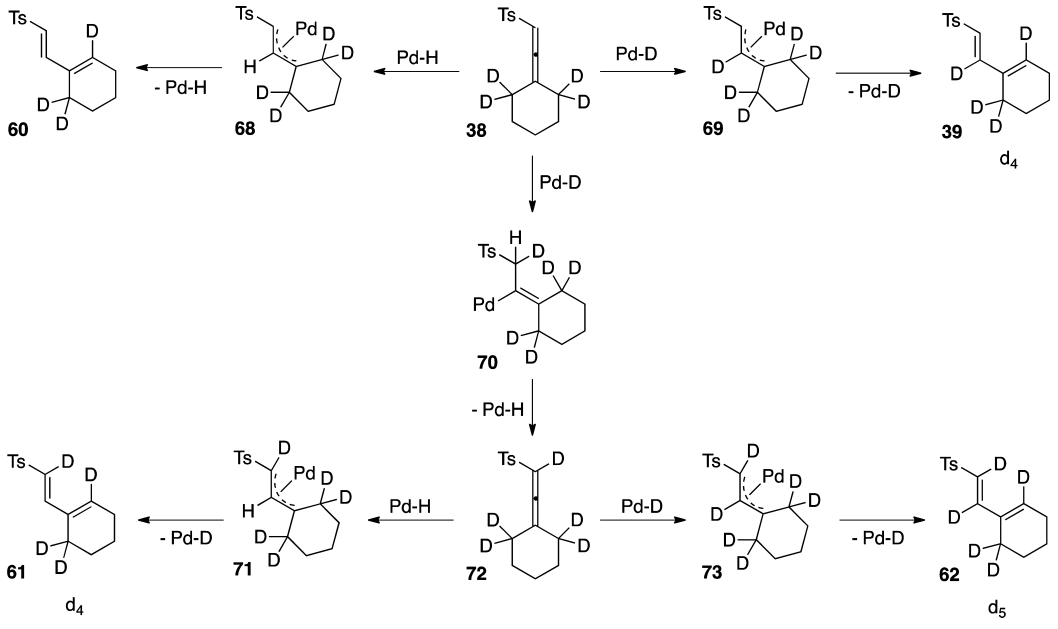


which yields a higher proportion of Pd–D to deuteropalladate (Figure 13). A simple kinetic isotope effect (KIE) wherein the protons are transferred before the deuteriums would lead to this result.

After observing the formation of an intermediate in the reaction in Figure 13, we wanted to see if the same type of intermediate was formed in the isomerization of a nondeuterated allene as well. The isomerization of the nondeuterated allene **78** was then monitored by ^{1}H NMR, using nonlabeled acetic acid, to see if the same intermediate was formed (Figure 14). The reaction proceeds more rapidly than the deuterated case, perhaps due to a kinetic isotope effect, and aliquots were taken at 15 min intervals. The faster rate of reaction made it more difficult to determine whether an intermediate species was being formed, but as the allene was consumed, the allenic proton (labeled as proton 6, Figure 14) decreased and the formation of two new products was seen. The same intermediate was formed and could be seen at the 15 min time point where there is a small doublet (labeled as Int = intermediate, Figure 14) that is overlapping with the vinylic cyclohexyl proton on the diene product being formed (labeled as proton 9, Figure 14).

It is known that palladium species can be susceptible to nucleophilic attack, especially by acetate ions.[20] We proposed that the intermediate being formed was the reversible trapping

Scheme 15. Generation of Diene Isotopologues Stemming from 38



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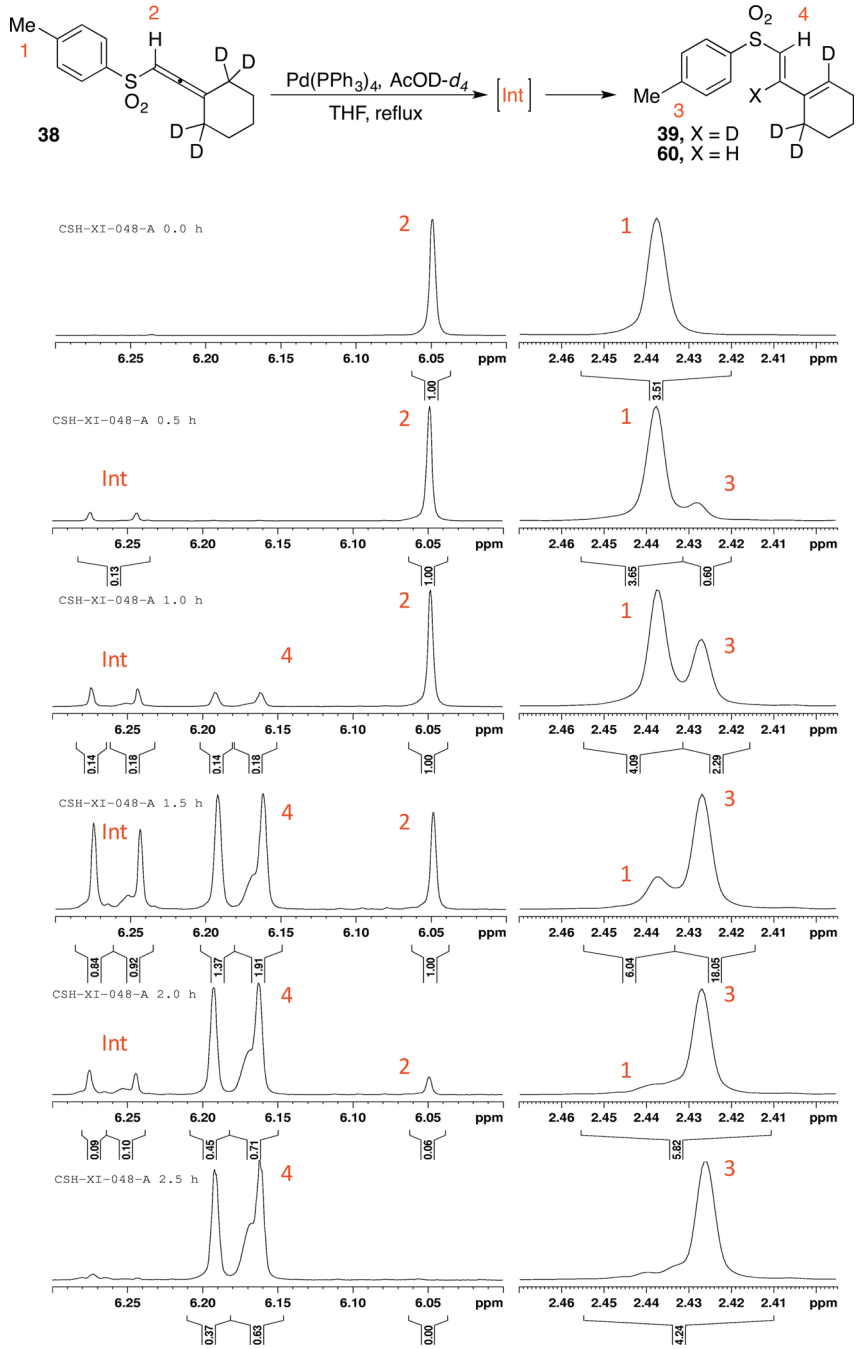

Figure 13. Monitoring the reaction of **38** by ^{1}H NMR.

of the palladium species by the acetate ion from acetic acid. To examine this conjecture, the allylic acetate **82** was prepared to compare with the intermediate observed in the reactions monitored by ^{1}H NMR. The allylic acetate **82**, corresponding to the nondeuterated diene **18**, was prepared as shown in Scheme 17 from **81**, whose preparation from 1-ethynylcyclohexanol **79** has been reported.[21] The allylic acetate clearly matches the ^{1}H NMR peaks of the intermediate with a doublet at 6.27 ppm and a singlet at 2.43 ppm and is presumed to be present in the reaction.

Acetate **82** was then treated under the palladium isomerization reaction conditions to ensure that this species does lead to product formation, and the conversion was completed quickly, giving **18** in 63% yield (Scheme 18) and demonstrating that an allylic acetate as an intermediate is feasible. This establishes the occurrence of the reversible acetate trapping of a π-allyl palladium intermediate formed in the isomerization of allenic sulfones to 1-arylsulfonyl 1,3-dienes.

An amended version of the mechanism now includes the reversible hydropalladation/β-hydride elimination in which the α-proton may be exchanged through **83**. It also includes the reversible trapping of a π-allyl palladium species by acetate anions to give **84** in solution (Scheme 19).

CONCLUSIONS

The palladium-catalyzed mechanism is more complex than that which was initially proposed. A distribution of deuterium throughout the dienyl products with the incorporation of additional

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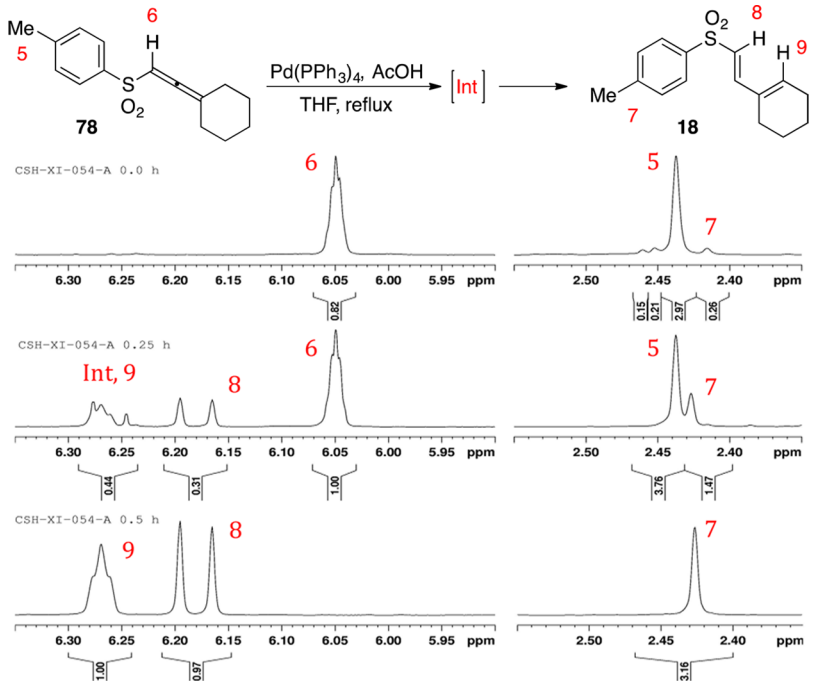
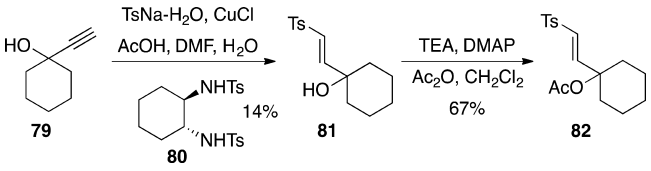
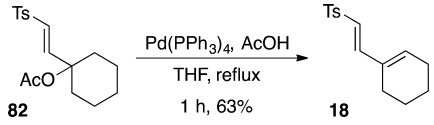


Figure 14. Monitoring the reaction of 77 by ^{1}H NMR.

Scheme 17. Preparation of 82

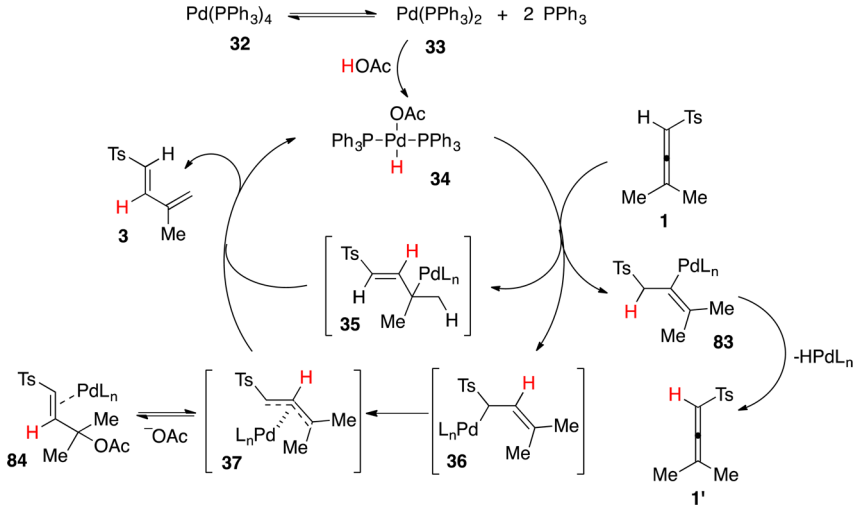


Scheme 18. Reaction of 82 To Yield 18



protons led to the proposal of the formation of a palladium hydride/deuteride[22] that is stable enough to not be destroyed in the time required for exchange of product olefin for new reactant allene. In addition, the hydro-/deuteropalladation is a reversible process whose rate is delicately balanced with that of the rate of isomerization, allowing interchange of hydrogen or deuterium among the exchangeable positions in the molecule, accounting for the distribution of deuterium in the labeled cases. The formation of an allylic acetate intermediate in this reaction supports the proposition that a π-allyl palladium species is a contributing factor in this mechanism that can be trapped by nucleophiles. The two mechanistic proposals by Cruikshank and Davies of a π-allyl palladium complex and a σ-alkyl complex are likely both in effect and the σ to π interchanges are more rapid than the isomerization processes and therefore lead to the formation of multiple products simultaneously with a distribution of deuterium throughout the available exchangeable sites.

Scheme 19. Amended Mechanism for the Palladium-Catalyzed Isomerization



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EXPERIMENTAL SECTION

General Information. All reactions were carried out in oven-dried glassware. Solvents were distilled by standard methods. Analytical thin-layer chromatography was performed on glass-backed silica gel plates with a fluorescent UV indicator. Column chromatography was carried out using 230−400 mesh silica gel with HPLC grade solvents. ^{1}H NMR spectra were recorded on either a 300 or 500 MHz spectrometer (s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, etc.). ^{13}C NMR spectra were obtained on the same instruments at 75 and 125 MHz, respectively, in $CDCl_3$ solution with tetramethylsilane (δ 0.00 ppm, ^{1}H spectra) or $CDCl_3$ (77.0 ppm, ^{13}C spectra) as an internal reference. Melting points are uncorrected. Infrared spectra were recorded on a FT-IR spectrometer with sodium chloride salt plates. High-resolution mass spectra were performed on a FTICR-MS with ESI.

Palladium Acetate Catalyzed Allene Isomerization. *(E)-1-((3-Methylbuta-1,3-dien-1-yl)sulfonyl)-4-(trifluoromethyl)benzene (**26**).* In an oven-dried round-bottom flask under an argon balloon, palladium acetate (0.006 g, 0.027 mmol, 10 mol %) and tricyclohexylphosphine (0.015 g, 0.054 mmol, 20 mol %) were dissolved in dry THF (2.7 mL). Then 1-((3-methylbuta-1,2-dien-1-yl)sulfonyl)-4-(trifluoromethyl)-benzene (**23**; 0.075 g, 0.272 mmol) was placed in the reaction flask and heated to reflux. Upon complete conversion of starting material by TLC (15% EtOAc/85% hexanes), the reaction mixture was cooled to room temperature. Water was placed in the reaction flask, and the mixture was extracted three times with CH_2Cl_2. The organic layers were combined and washed with water and brine. The solution was dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation. The crude product was purified by column chromatography (5% EtOAc/95% hexanes) to give **26** (0.039 g) as an oil in 53% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 8.7 Hz, 2H), 7.81 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 15.0 Hz, 1H), 6.31 (d, J = 15.0 Hz, 1H), 5.52 (s, 1H), 5.50 (s, 1H), 1.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 144.4, 138.6, 135.0 (q, J = 19.5 Hz), 128.2, 127.9, 126.9, 126.5 (q, J = 2.25 Hz), 123.2 (q, J = 163.5 Hz), 18.0; IR (cm^{-1}) 3058, 2983, 2923, 1724, 1604, 1402, 1322, 1159, 1108, 1060, 1012, 965, 845, 758, 710, 603; HRMS m/z calcd for $(C_{12}H_{11}F_3O_2S)Na^+$ 299.0324, found 299.0325.

*(E)-1-((3-Methylbuta-1,3-dien-1-yl)sulfonyl)-3,5-bis-(trifluoromethyl)benzene (**28**).* The product was prepared by a method similar to that for **26** and was isolated as an oil in 83% yield (0.083 g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 2H), 8.11 (s, 1H), 7.47 (d, J = 15.0 Hz, 1H), 6.32 (d, J = 15.0 Hz, 1H), 5.59 (s, 1H), 5.57 (s, 1H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 143.8, 138.5, 133.2 (q, J = 33.8 Hz), 128.9, 128.0 (m), 126.9 (m), 125.98, 122.4 (q, J = 272.5 Hz), 18.0; IR (cm^{-1}) 3082, 2058, 2927, 2856, 1620, 1584, 1358, 1330, 1279, 1187, 1144, 1104, 977, 905, 850, 810, 758, 695, 679, 631, 583; HRMS m/z calcd for $(C_{13}H_{10}F_6O_2S)Na^+$ 367.0198, found 367.0197.

*(E)-1-((2-(4,4-Dimethylcyclohex-1-en-1-yl)vinyl)sulfonyl)-3,5-bis-(trifluoromethyl)benzene (**30**).* The product was prepared by a method similar to that for **26** and was isolated as an oil in 83% yield (0.083 g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 2H), 8.09 (s, 1H), 7.39 (d, J = 15.0 Hz, 1H), 6.37−6.31 (m, 1H), 6.19 (d, J = 15.0 Hz, 1H), 2.14−2.02 (m, 4H), 1.45 (t, J = 6.6 Hz, 2H), 0.92 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 144.4, 143.3, 133.1 (q, J = 33.8 Hz), 132.1, 127.9 (m), 126.6 (m), 122.4 (q, J = 272.5 Hz), 121.9, 40.6, 34.5, 28.8, 28.0, 22.0; IR (cm^{-1}) 3086, 3054, 3027, 2955, 2923, 2864, 1628, 1584, 1362, 1330, 1279, 1139, 1100, 973, 905, 854, 762, 695, 679, 627; HRMS m/z calcd for $(C_{18}H_{18}F_6O_2S)Na^+$ 435.0824, found 435.0825.

Phosphine Effect on the Palladium Acetate Catalyzed Reaction. In an oven-dried round-bottom flask under an argon balloon, palladium acetate (0.006 g, 0.029 mmol, 10 mol %) and triphenylphosphine (0.015 g, 0.058 mmol, 20 mol %) were dissolved in dry THF (2.7 mL). Then 1-((3-methylbuta-1,2-dien-1-yl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (**24**; 0.100 g, 0.291 mmol) was placed in the reaction flask and heated to reflux. Upon complete conversion of starting material by TLC (15% EtOAc/85% hexanes) the reaction mixture was cooled to room temperature. Water was placed in the reaction flask and the mixture was extracted three times with CH_2Cl_2. The organic layers were combined and washed with water and brine. The solution was dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation. The crude product was purified by column chromatography (5% EtOAc/95% hexanes) to give **29** (0.063 g) as an oil in 63% yield.

General Procedure for Isomerization. In an oven-dried round-bottom flask with an argon balloon were placed the palladium catalyst (10 mol %, unless stated otherwise), acid cocatalyst (10 mol %, unless stated otherwise), and dry solvent (0.1 M, unless stated otherwise). Then the allenic sulfone was placed in the reaction flask and heated to reflux. The reaction was monitored by TLC (15% EtOAc/85% hexanes). Either upon reaction completion or prolonged reaction time with no change in TLC, the reaction mixture was cooled to room temperature. Water was placed in the reaction flask, and the mixture was extracted three times with CH_2Cl_2. The organic layers were combined and washed with water and brine. The solution was dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography to isolate **3** (5% EtOAc/95% hexanes).

Incorporation of Deuterium into 1. In an oven-dried round-bottom flask were placed deuterated acetic acid (0.029 g, 0.450 mmol), $Pd(PPh_3)_4$ (0.15g, 0.135 mmol, 30 mol %), and 5 mL of dry THF. Then **1** (0.100 g, 0.450 mmol) in 4 mL of dry THF was added. The reaction mixture was heated to reflux under argon and monitored by TLC (15% EtOAc/85% hexanes). After reaction completion, the solution was cooled to room temperature and diluted with CH_2Cl_2. To the solution was added silica gel, and the mixture was evaporated by rotary evaporation. The solid mixture was subjected to column chromatography for purification to yield a **3**:**40**:**41** mixture in a ratio of 0.66:0.14:0.20 in 83% yield (0.083 g).

Preparation of 38. *2,2,6,6-Tetradeuterocyclohexan-1-one (**57**).*[23] Cyclohexanone (1.5 g, 15.28 mmol), potassium carbonate (4.27 g, 30.56 mmol), and D_2O (5 mL) were refluxed for 24 h. The ketone (top layer) was separated from the aqueous layer via a separatory funnel and evaluated by ^{1}H NMR. The process was repeated by adding 5 mL of D_2O and 4.3 g of potassium carbonate to the product and refluxing for 24 h again. The ketone **57** was separated from the aqueous layer, isolated in 78% yield, and evaluated by ^{1}H NMR.

*2,2,6,6-Tetradeutero-1-ethynylcyclohexan-1-ol (**58**).*[24] In a flame-dried round-bottom flask purged with argon was placed dry THF (75 mL). The solution was cooled to −78 °C in a dry ice/acetone bath and ethynylmagnesium chloride (53.5 mL, 26.74 mmol, 0.5 M in THF) was added. Then a solution of **57** (2.1 g, 20.57 mmol) in 25 mL of dry THF was placed dropwise in the reaction flask. The reaction mixture was stirred overnight and then quenched with water. The mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation. The alcohol **58** was isolated as a liquid (1.41 g) in 51% yield.

*1-Ethynyl-2,2,6,6-tetradeuterocyclohexyl 4-Methylbenzenesulfinate (**59**).* In a flame-dried round-bottom flask under an argon atmosphere, *p*-toluenesulfonyl chloride (1.0 equiv) was dissolved in CH_2Cl_2 (0.05 M) and triethylamine (1.1 equiv) was added. A solution of **58** (1.0 equiv) and triphenylphosphine (1.0 equiv) in CH_2Cl_2 was added dropwise to the reaction solution over 20 min. The reaction mixture was stirred at room temperature and monitored by TLC until consumption of sulfonyl chloride. The reaction mixture was concentrated and a diethyl ether/hexanes solution (1/4) was added and swirled vigorously to induce precipitation of triethylamine hydrochloride. The mixture was filtered through silica gel in a sintered-glass funnel and washed with diethyl ether, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography (3% EtOAc/97% hexanes) to give **59** as a white solid in 32% yield (0.92 g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 2.84 (s, 1H), 2.41 (s, 3H), 1.80−1.50 (m, 5H), 1.34−1.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 142.2, 129.5, 124.9, 83.7, 78.9, 71.9, 38.5−37.9 (m), 24.6, 22.5, 22.4, 21.4.

*1-Methyl-4-((2-(2,2,6,6-tetradeuterocyclohexylidene)vinyl)-sulfonyl)benzene (**38**).* To a solution of the sulfinate ester **59** in CH_2Cl_2 (0.05 M) under an argon atmosphere was added silver hexafluoroantimonate (2 mol %). The reaction mixture was stirred at room

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temperature and monitored by TLC until complete conversion of starting material. The reaction mixture was filtered through silica gel in a sintered-glass funnel, rinsing with more CH_2Cl_2, and the filtrate was concentrated in vacuo to give **38** as a white solid in 97% yield (0.893 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.05 (s, 1H), 2.44 (s, 3H), 1.61−1.46 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 135.6, 129.6, 127.7, 98.9, 77.2, 26.4, 25.3, 21.6; HRMS m/z calcd for $(C_{15}H_{14}D_4O_2S)Na^+$ 289.1171, found 289.1171.

Isomerization of 38. In a clean oven-dried 25 mL round-bottom flask with a stir bar was placed 2−3 mL of D_2O, which was refluxed for 3 h. The flask was then cooled to room temperature and the D_2O removed via pipet. Fresh D_2O was then placed in the flask and refluxed for an additional 2 h. Again the flask was cooled to room temperature and the D_2O removed. Fresh D_2O was added for a third time and refluxed for 1.5 h. The flask was cooled to room temperature and the D_2O removed. The flask was then dried in the oven overnight at 115 °C and cooled in a desiccator. The reflux condenser was capped to prevent water adsorption overnight. In the reaction flask were placed acetic acid-d_4 (0.002 g, 0.038 mmol), dry THF (7.5 mL), $Pd(PPh_3)_4$ (0.043 g, 0.038 mmol), and **38** (0.100 g, 0.376 mmol). The mixture was heated to reflux using the same condenser as above for 6 h. The reaction mixture was then cooled to room temperature, quenched with 2 mL of D_2O, and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous sodium sulfate and concentrated by rotary evaporation. The crude material was purified by column chromatography (6−8% EtOAc/92−94% hexanes).

Monitoring the Reaction of 38 by ^{1}H NMR. Acetic acid-d_4 (0.002 g, 0.038 mmol) was placed in a D_2O refluxed round-bottom flask followed by $Pd(PPh_3)_4$ (0.043 g, 0.038 mmol) and dry THF (9 mL). The solution was swirled and became bright yellow, and then **38** was added. Immediately, 0.5 mL of the solution was removed via syringe. The contents of the flask were heated to reflux. The removed aliquot was filtered through a microscale column made from a glass pipet (filled with a cotton plug, sand, and silica gel). The material was washed through with CH_2Cl_2 (~5 mL). The collected filtrate was concentrated by rotary evaporation and crude ^{1}H NMR was taken. The process of removing 0.5 mL aliquots was repeated every 30 min. The remaining material after 2.5 h at reflux was treated with silica gel and concentrated on the rotary evaporator and then purified by column chromatography (5% EtOAc/95% hexanes).

The same procedure was followed for monitoring the reaction of **72** by ^{1}H NMR, except that nondeuterated acetic acid was used and aliquots were removed every 15 min.

Preparation of 82. The diamine **80** was prepared by literature methods[25] in 77% yield (0.287 g).

The following procedure is a variation of a literature method.[21] To a mixture of copper(I) chloride (0.004 g, 0.040 mmol), the diamine **80** (0.017 g, 0.040 mmol), and sodium *p*-toluenesulfinate (0.158 g, 0.886 mmol) in DMF (0.3 mL), H_2O (0.3 mL), and glacial acetic acid (0.3 mL) was added the propargyl alcohol **79** (0.100 g, 0.805 mmol), and the mixture was heated to 60 °C with a condenser open to the air and stirred for 18 h. After this time the residue was dissolved in Et_2O and the solution was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation. The product **81** was purified by column chromatography (18% EtOAc/82% hexanes) and isolated in 14% yield (0.032 g). Spectral data matched reported literature data.

(E)-1-(2-Tosylvinyl)cyclohexyl Acetate (82). The alcohol **81** (0.026 g, 0.093 mmol) was dissolved in triethylamine (2.2 mL) and CH_2Cl_2 (1 mL), and DMAP was added (0.001 g, 0.009 mmol). Next, acetic anhydride (0.088 mL, 0.927 mmol) was added and the reaction mixture was stirred at room temperature for 2 days. The reaction mixture was diluted with CH_2Cl_2 after completion by TLC (30% EtOAc/70% hexanes). The mixture was washed with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with CH_2Cl_2 twice more. The combined organic layers were washed with dilute HCl, water, and brine. The combined organic layers were dried over anhydrous sodium sulfate and concentrated by rotary evaporation. The crude material was purified by column chromatography (15% EtOAc/85% hexanes) to produce **82** as a white solid (mp =88−90 °C) in 67% yield (0.020 g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 15.5 Hz, 1H), 6.26 (d, J = 15.5 Hz, 1H), 2.43 (s, 3H), 2.17 (broad, 2H), 2.03 (s, 3H), 1.67−1.44 (m, 7H), 1.32−1.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 149.4, 144.3, 137.3, 129.8, 128.3, 127.6, 79.6, 34.3, 24.9, 21.6, 21.5, 21.4; IR (cm^{-1}) 3027, 2933, 2860, 1736, 1446, 1364, 1319, 1266, 1229, 1148, 1086, 1013, 960, 813, 751, 669; HRMS m/z calcd for $(C_{17}H_{22}O_4S)Na^+$ 345.1131, found 345.1129.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00880.

^{1}H NMR and ^{13}C NMR for all novel compounds (PDF)

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Notes

The authors declare no competing financial interest.

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