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

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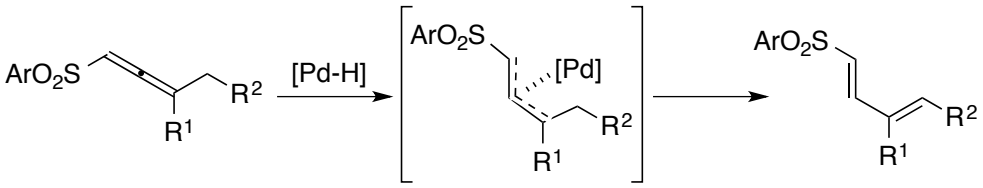
Abstract

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

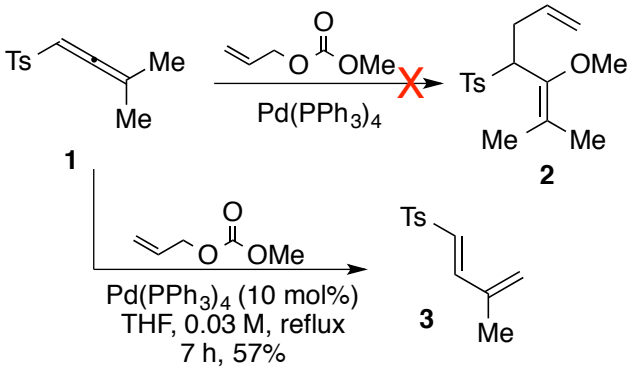


Introduction

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 as compared 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 chemistries in our group,[4] we were interested in generating an alkoxyallylic sulfone of the type **2** via a process shown in Scheme 1. In the event, the reaction of **1** in the presence of tetrakis(triphenylphosphine)palladium(0) led to an isomerization of the allenic sulfone to a 1-arylsulfonyl-1,3-diene **3**. We recently reported the initial discovery of this reaction.[4a]

Scheme 1. Attempted alkoxyalkylation of an allenic sulfone

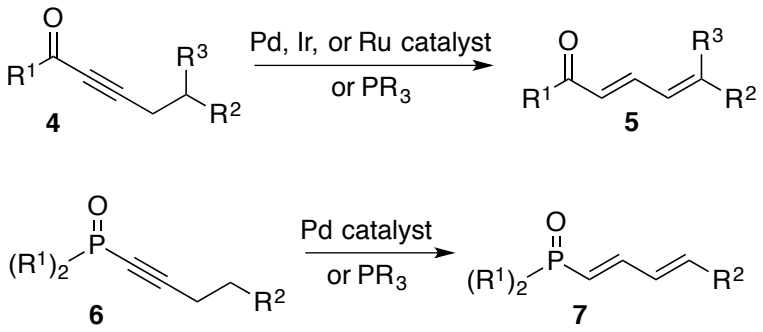


In 1988, the isomerization of acetylenic alkynones to conjugated (*E,E*)-dienones was reported by the Trost group employing palladium catalysis, and by the Lu group

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 similar allenyl intermediates as part of the mechanism that were similar to those reported by Suzuki and Moro-Oka 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).

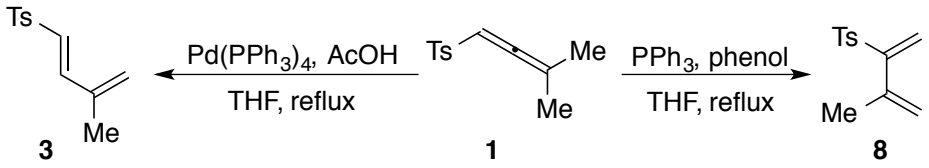
Scheme 2. Isomerization of acetylenic carbonyl and phosphorus compounds.



When simple phosphine catalysis is applied to allenic sulfones, a regioisomeric 2-substituted diene is produced (Scheme 3); 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 either as an anionic stabilizing group or a leaving group.[3c, 3h, 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.

Scheme 3. Regiodivergent reactions of allenic sulfones



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.

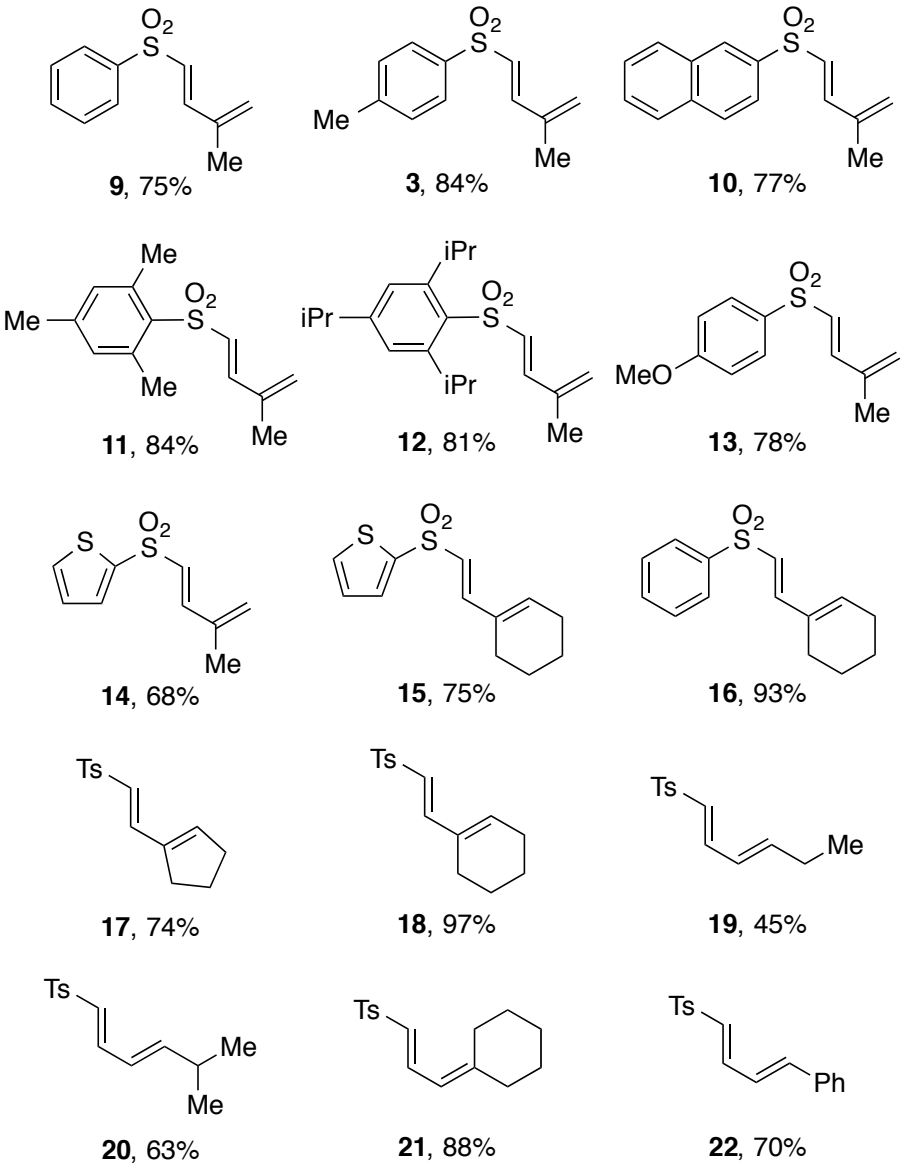


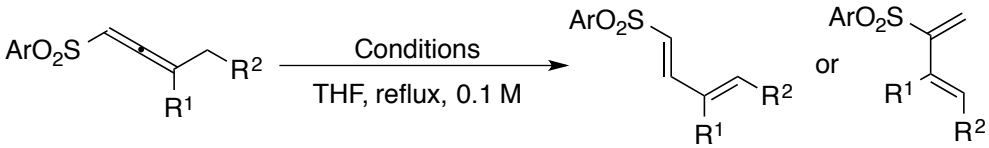
Figure 1. 1-Arylsulfonyl 1,3-dienes prepared via isomerization by palladium catalysis.

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% yield, respectively

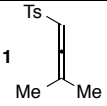
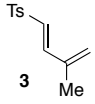
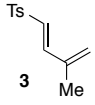
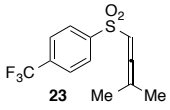
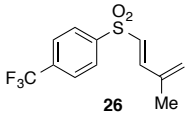
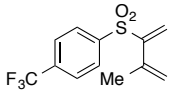
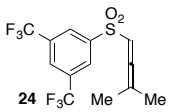
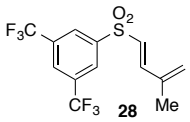
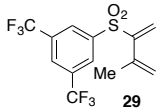
(Table 1, entries 4 and 6). Additionally, with allene **25**, the reaction afforded a 54% yield of an inseparable mixture of the expected product **30** as well as the corresponding 2-arylsulfonyl 1,3-diene **31** in a 1:4 ratio (Table 1, entry 8). These outcomes are the result of the nucleophilic reaction 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. Based on 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 larger cone angle than 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 tricyclohexyphosphine 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 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 hours 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

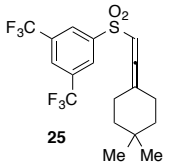
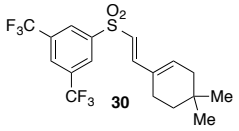
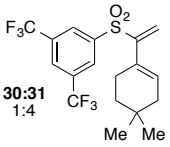
conditions (Condition A) whereas the previous results with $Pd(PPh_3)_4$ gave the 2-substituted dienes or mixtures of dienes (Condition B). As we had previously shown that the isomerization could be executed in the presence of $Pd(OAc)_2/PPh_3$ as the catalyst system,[4a] it is worthy to note that when **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.

Table 1. Isomerization of electron-withdrawing allenic sulfones.

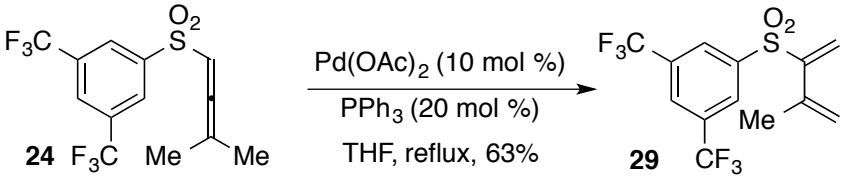


Condition A: $Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%)
Condition B: $Pd(PPh_3)_4$ (10 mol%), AcOH (10 mol%)

Entry	Substrate	Condition	Time	Product	Yield (%)
1	 **1**	A	2.3 h	 **3**	83
2	**1**	B	20 m	 **3**	84
3	 **23**	A	3 h	 **26**	53
4	**23**	B	20 m	 **27**	56
5	 **24**	A	3 h	 **28**	83
6	**24**	B	25 m	 **29**	61

7		A	2 h	 83
8	**25**	B	40 m	 54

Scheme 4. Reaction of **24** with palladium acetate and triphenylphosphine.

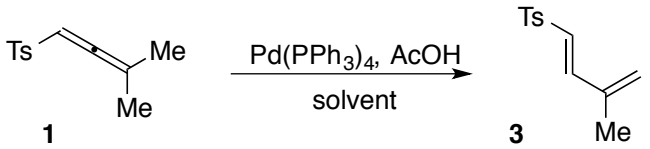


After initial demonstration of the isomerization of allenic sulfones to 1-arylsulfonyl 1,3-dienes by palladium catalysis, further examination of the reaction conditions to improve both the yield and efficiency of the reaction was pursued. The results obtained previously[4a] showed in general that a combination 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 2-3). 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 4-5). Dimethylformamide (DMF) and *t*-butyl methyl ether (TBME) were also suitable, but not as efficient (Table 2, entries 6-7). 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).

Table 2. Solvent effects on the palladium-catalyzed isomerization.[(a)]

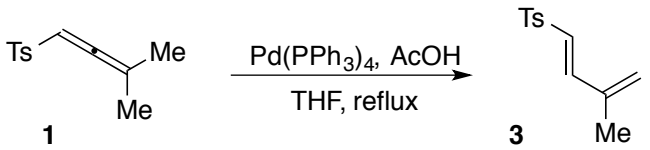


Entry	Solvent	Temp (°C)	Time	Yield (%)
1	THF	65	20 min	84
2	Toluene	80	20 min	75
3	MeCN	82	25 min	80
4	DMPU[(b)]	80	20 min	56
5	Dimethylcarbonate	90	25 min	58
6	DMF[(c)]	80	1h 40min	60
7	TBME[(d)]	55	8 h	80
8	CH_2Cl_2	40	25 h	[(e)]

[(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 = *t*-butyl methyl ether [(e)] **1** was recovered in 59% yield.

After determining that THF was the best solvent for this isomerization, the effect of catalyst loading on the reaction time and yield was evaluated. 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 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).

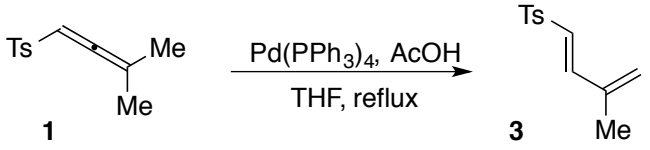
Table 3. Effects of catalyst loading on the palladium-catalyzed isomerization.[(a)]



Entry	Catalyst Loading (mol%)	Temp (°C)	Time	Yield (%)
1	2.5	65	25 min	83
2	5.0	65	25 min	88
3	10.0	65	20 min	84

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

Table 4. Concentration effects on the palladium-catalyzed isomerization.[(a)]



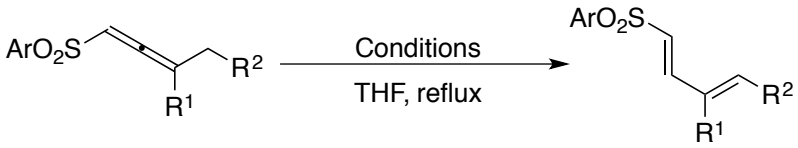
Entry	Concentration (M)	Temp (°C)	Time	Yield (%)
1	0.025	65	20 min	88
2	0.05	65	20 min	81
3	0.10	65	20 min	84
4	0.15	65	25 min	86

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

After these studies with **1**, attempts at combining some of the different reaction conditions were examined and it was found that under a catalyst loading of 2.5 mol%, 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 one hour 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 when treated 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) compared to the previous reaction conditions (Table 5, entries 3 and 5). For diene **20**, the starting allene and product diene have identical Rf values, so ascertaining exactly when the reaction completion occurred was fallible. However, the reaction was still complete within the 2 hour reaction time period and produced an almost identical yield of 65% (Table 5, entries 7-8). 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.

Table 5. Comparison of reaction conditions.



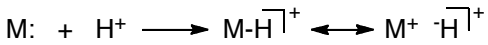
Condition A: $Pd(PPh_3)_4$ (10 mol%), AcOH (10 mol%), 0.1 M
Condition B: $Pd(PPh_3)_4$ (2.5 mol%), AcOH (2.5 mol%), 0.05 M

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

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

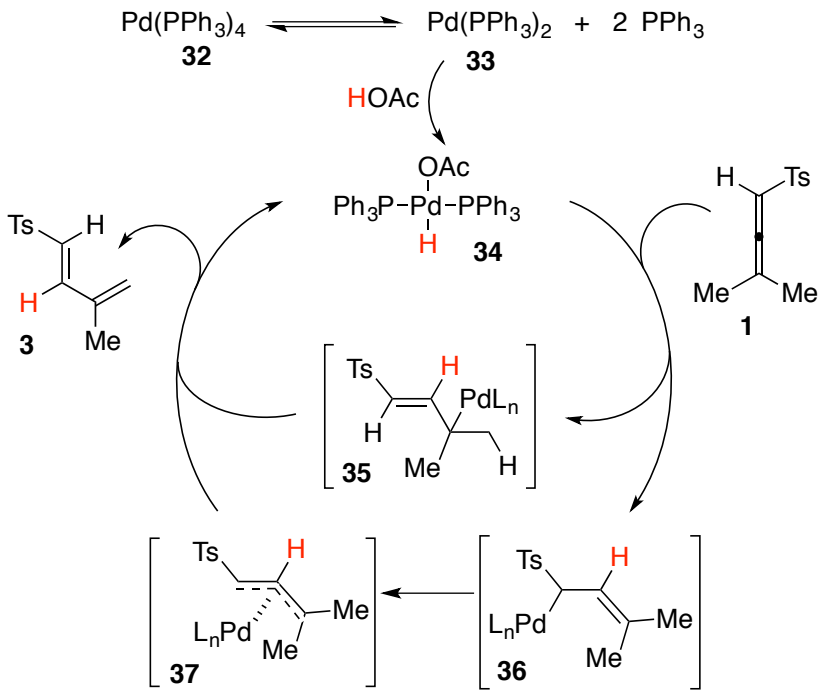
hydrides to perform this function. Protonation of low-valent transition metals generates a class of reagents that contain a M-H bond. This bond may function differently from typical conjugate acids in that it may act as a hydridometal species rather than a protonated metal.[16] (Eq 1) As observed in many metal protonation/metal hydride complexes, umpolung of the 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 hydrometallations/β-hydride eliminations, presumably through an allenyl intermediate, eventually led to an *E,E*-diene.[5, 7, 12]



(Eq. 1)

On this basis and the data obtained initially, we proposed the mechanism shown in Scheme 6 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.

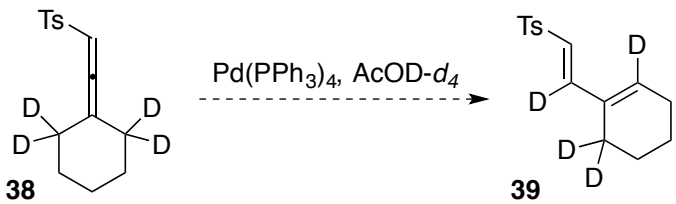


Deuterium Labeling

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 based on 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.

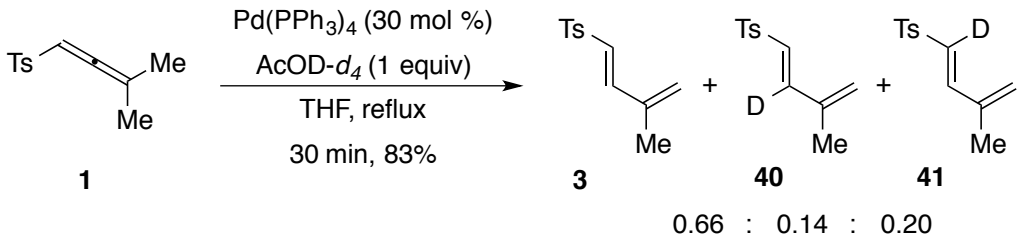
Scheme 6. Proposed isomerization of deuterated allene **38**.



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 hydropalladation/β-deuteride elimination?, 3) would deuterium be incorporated into a non-deuterated diene after formation by exposure to AcOd-d_4 alone or to the $Pd(PPh_3)_4$/AcOD-d_4 reaction conditions?, and 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 one equivalent 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 reversible H/D exchange by deuteropalladation/β-hydride elimination.

Scheme 7. Incorporation of deuterium into **1**.



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 protons, leaving the remaining integrated area to the α-proton of **40** which is 0.14 protons (Figure 2).
- As the the α proton of **3** integrates for 0.66 protons, the β-proton of **3** will also be 0.66 protons.

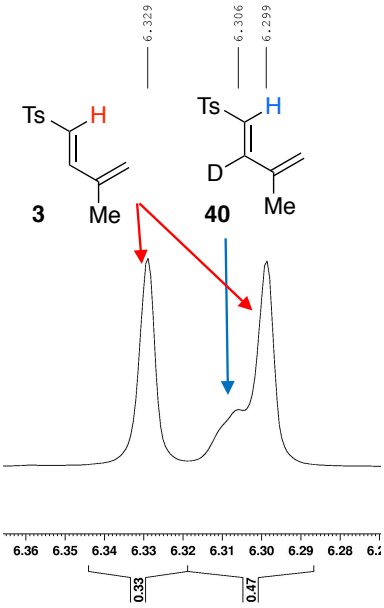


Figure 2. α Proton signals for **3** and **40**.

- 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 protons, which leaves the remainder of the integrated signal at 7.30 ppm (0.20 protons) to the β-H of **41**.

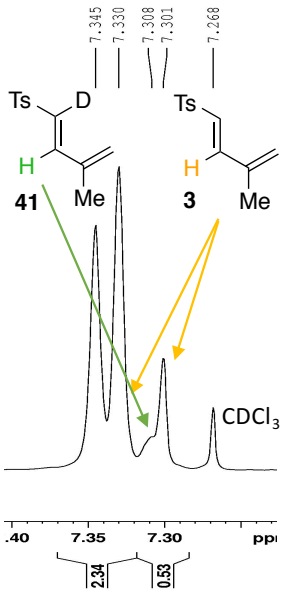


Figure 3. β Proton signals of **3** and **41**.

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

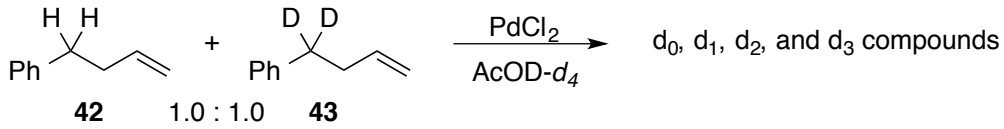
Thus, this reaction also illustrated the ability of the α-position of the allenic sulfone to be exchanged. A faster rate of hydropalladation than deuteropalladation would explain the very small amount of deuterated products that were observed.

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

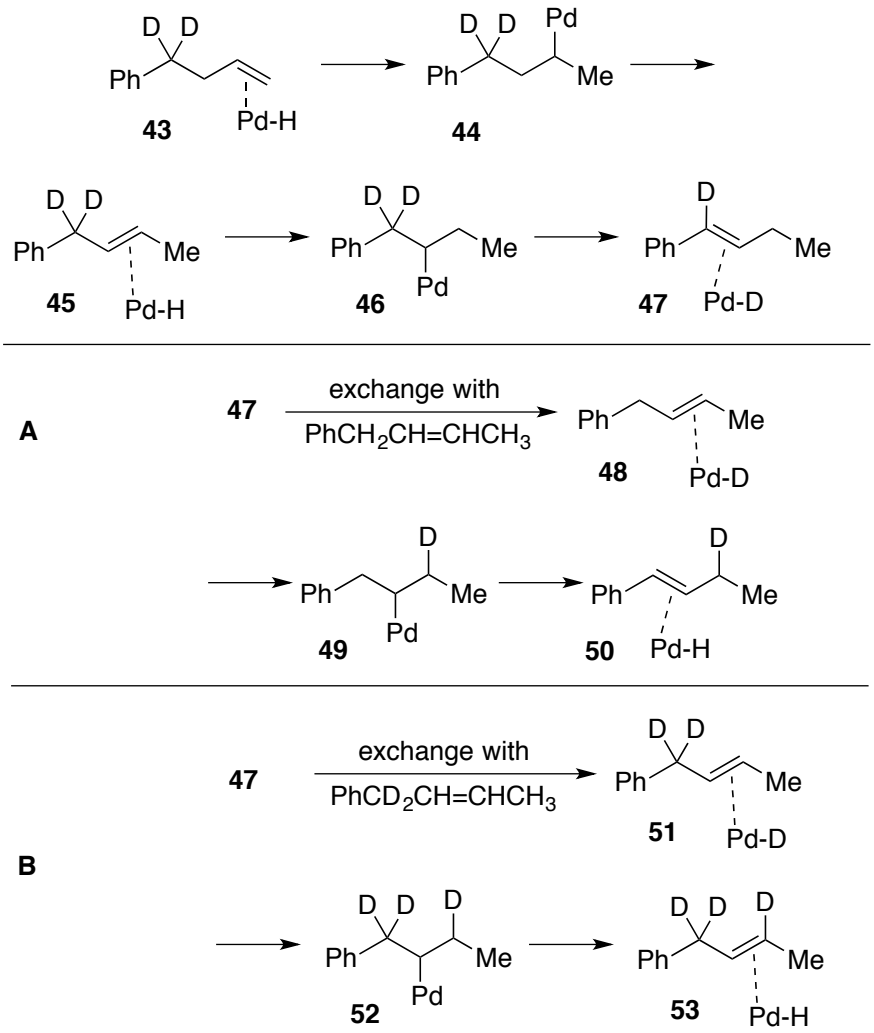
Cruikshank and Davies also note that when a mixture of d_0 and d_2 isotopologues are mixed and isomerized there is formation of both d_1 and d_3 products in addition to the expected d_0 and d_2 products (Scheme 8).

Scheme 8. Deuterium transfer between alkenes.[17a]

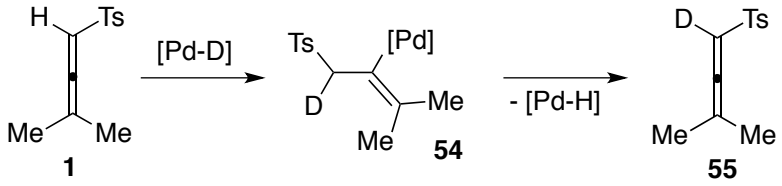


This indicates that a deuterium from a d_2 deuterated alkene has been transferred to a d_0 molecule to generate the d_1 species, or to another d_2 molecule to generate the d_3 species (Scheme 9).[17a] It is by a method similar to this that the α-hydrogen of the allenic sulfone can be exchanged for a deuterium atom (Scheme 10).

Scheme 9. Mechanism for deuterium transfer between alkenes.[17a]



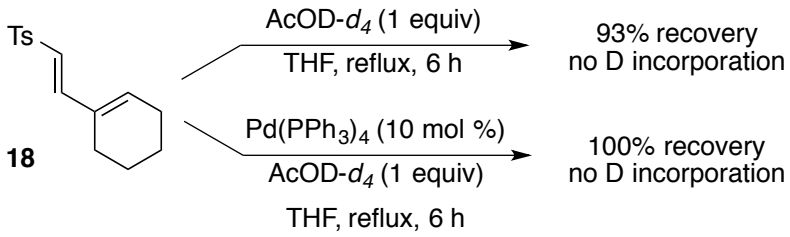
Scheme 10. α-Proton exchange of an allenic sulfone.



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 non-deuterated diene **18** was treated with one equivalent of deuterated acetic acid at reflux for 6 hours and there was no incorporation of deuterium into the diene observed. Then, **18** was subjected to a

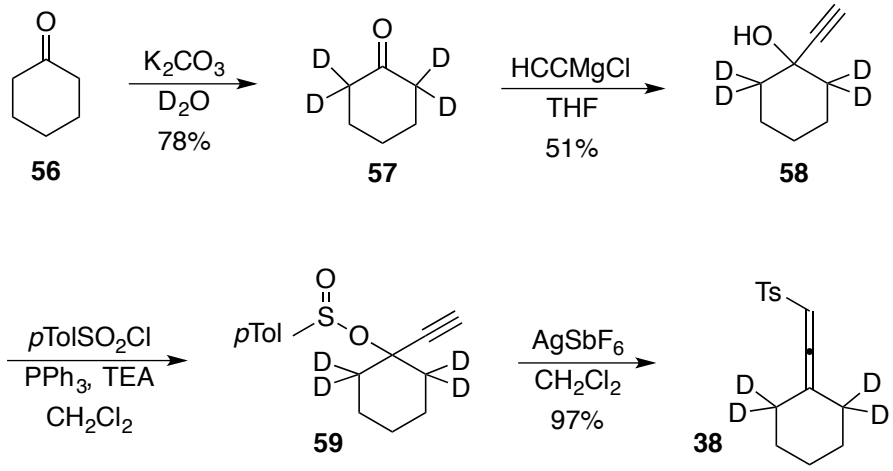
mixture of $Pd(PPh_3)_4$ and AcOD-d_4 at reflux for 6 hours (Scheme 11). There was also no incorporation of deuterium in this case, suggesting that deuteropalladation only occurs in the allene starting materials and not in the product dienes.

Scheme 11. Subjection of **18** to deuterium conditions.



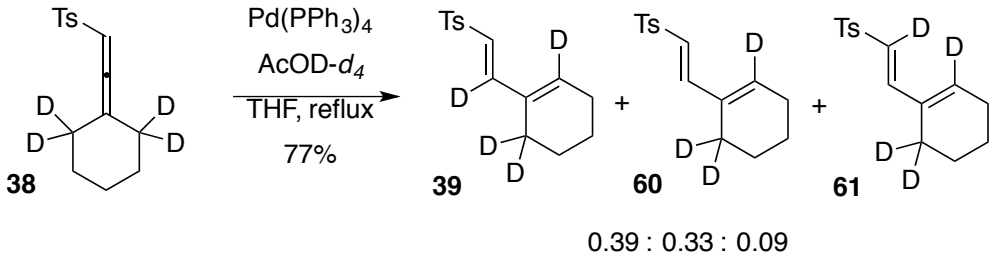
In order to examine the isomerization proposed in Scheme 7, we prepared allene **38** by the steps outlined in Scheme 12. Cyclohexanone was refluxed with potassium carbonate and deuterium oxide twice for 24 hours for α-exchange of the protons with deuteriums. The labeled cyclohexanone **57** was then 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.

Scheme 12. Preparation of the tetra-deuterated allene **38**.



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

Scheme 13. Isomerization of **38**.



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 8 and Figures 2-3.

- 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.

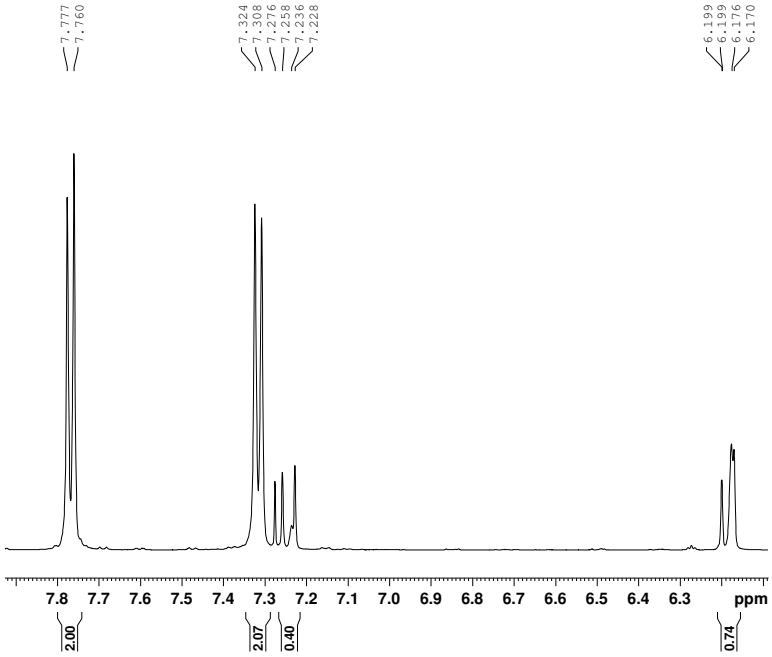


Figure 4. ^{1}H NMR overlapping peaks for reaction shown in Scheme 14.

- 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 **59**. This entire signal integrated for 0.74 protons.
- The signals for the β protons appear near 7.24 ppm. The singlet signal for the β proton of **60** overlapped with the right half of the doublet signal for the β proton of **39**. This entire signal integrated for 0.40 protons.
- 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 **59** (Figure 5). The area of the doublet of **59** was estimated to be 2.72 protons compared to the remaining integrated area for **39** equal to 2.86 protons.

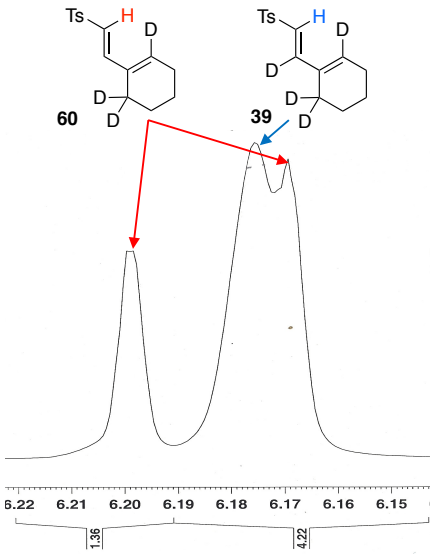


Figure 5. α Proton signals for **39** and **60.**

- For the β proton signals, the singlet signal for **60** overlapped with the right half of the doublet signal for the β proton of **59** (Figure 6). The area of the doublet of **59** was estimated to be 2.00 compared to the remaining integrated area for **60** equal to 0.73 protons.

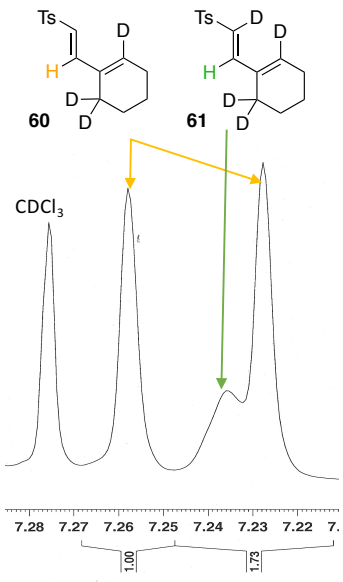


Figure 6. β Proton signals for **60** and **61.**

- A summary for this method gives a ratio of

α-**39** = 2.86		= 1.43
α-**59** = 2.72	→	= 1.36
β-**59** = 2.00		= 1.00
β-**60** = 0.73		= 0.365

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

Table 6. Computer-assisted analysis of the α-proton peaks.

Fit	Frequency		Width		Intensity	**Area**	%Lor. chisq	Peak
	ppm	Hz	ppm	Hz				
STD:	6.199	3100.26	0.00386	1.929	0.847	**8.140**	100.00	α-**157**
STD:	6.176	3088.82	0.00772	3.860	1.167	**22.441**	100.00	α-**150**
STD:	6.169	3085.41	0.00465	2.325	0.892	**10.329**	100.00	α-**157**

Table 7. Computer-assisted analysis of the β-proton peaks.

Fit	Frequency	Width	Intensity	**Area**	%Lor. chisq	Peak

	ppm	Hz	ppm	Hz				
STD:	7.258	3629.88	0.00404	2.023	0.897	**9.044**	100.00	β-**157**
STD:	7.236	3619.17	0.00737	3.687	0.228	**4.184**	100.00	β-**158**
STD:	7.228	3614.77	0.00386	1.932	0.964	**9.283**	100.00	β-**157**

- The total integrated area of the α-proton of **59** was 18.469 protons compared to the α-proton of **39** which was 22.441 protons.
- The total integrated area of the β-proton of **59** was 18.327 protons compared to the β-proton of **60** which was 4.184 protons.
- A summary for this method gives a ratio of

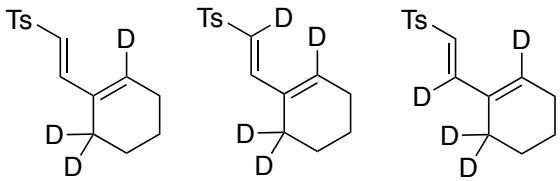
α-**39** = 22.441 = 1.22
α-**59** = 18.469 → = 1.01
β-**59** = 18.327 = 1.00
β-**60** = 4.184 = 0.228

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

$$\frac{\beta-\mathbf{59}}{0.40} = \frac{1.0}{1.228} \rightarrow 0.326 \qquad \frac{\beta-\mathbf{60}}{0.40} = \frac{0.228}{1.228} \rightarrow 0.074$$

$$\frac{\alpha-\mathbf{59}}{0.74} = \frac{1.01}{2.23} \rightarrow 0.335 \qquad \frac{\alpha-\mathbf{39}}{0.74} = \frac{1.22}{2.23} \rightarrow 0.405$$

The α-**59** and β-**59** correspond to the same molecule, and they are averaged together to approximate the ratio of compounds in the mixture (Figure 7).

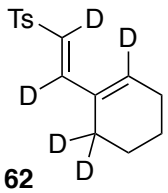


60 **61** **39**

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). 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 discernable 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.



62

Figure 8. Pentadeuterated diene **62.**

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 comparing to the ^{1}H NMR of the nondeuterated **18**) though integration of the same region indicated an integration of ~0.12 protons. A ^{2}H NMR also showed this position to be the only deuterated position in the molecule (Figure 9).

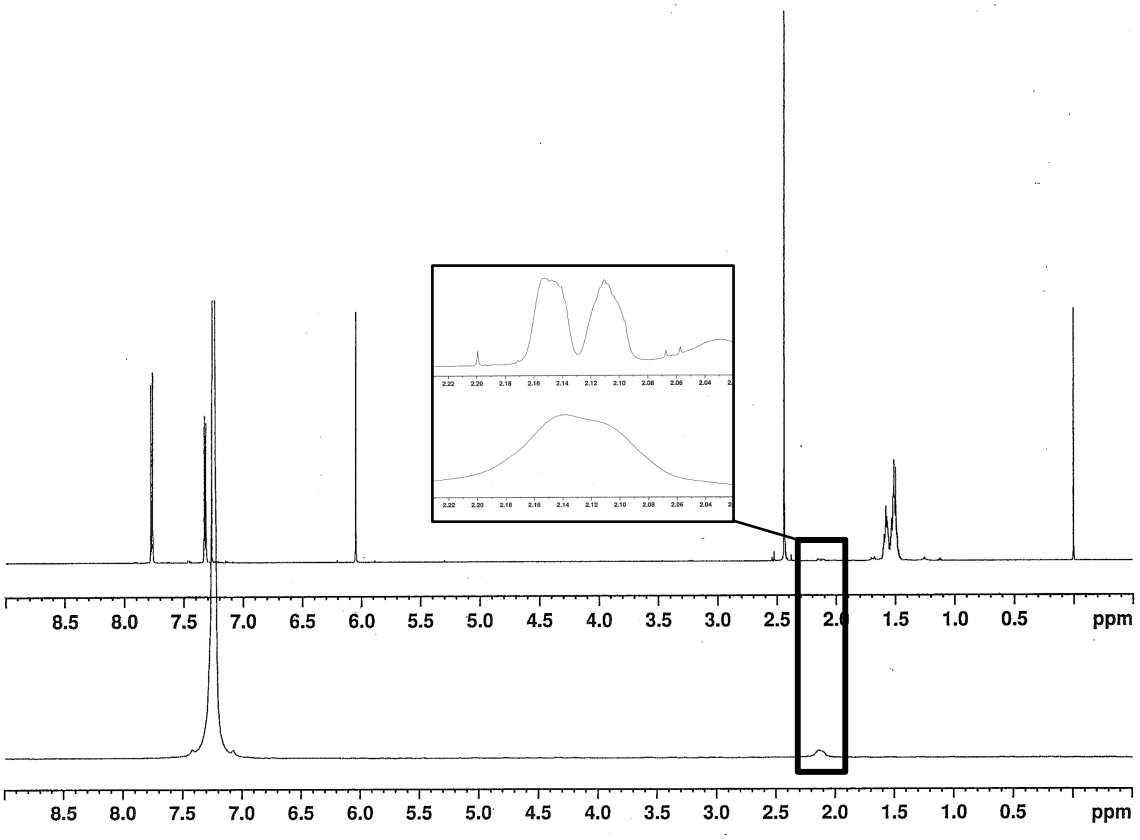


Figure 9. ^{2}H NMR vs. ^{1}H NMR comparison of **38**.

To further determine the extent of deuteration of the starting allene and the ratio of diene isotopologues in the product mixture, electronspray ionization mass spectrometry (ESI-MS) was taken 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 Equation 2.

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

where x = mass unit

$P(x)$ = probabililty of the mass unit

A^{13C} = relative abundance of ^{13}C, etc.

$\#^{13}$C = number of ^{13}C atoms in the molecule, etc.

${}_{\#13C}P_{15}$ is a permutation for how many different ways there are to insert $\#^{13}$C 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	Relative 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 theoretical isotopic cluster ratios we can extract the final ratios of the isotopologues in the mixture.

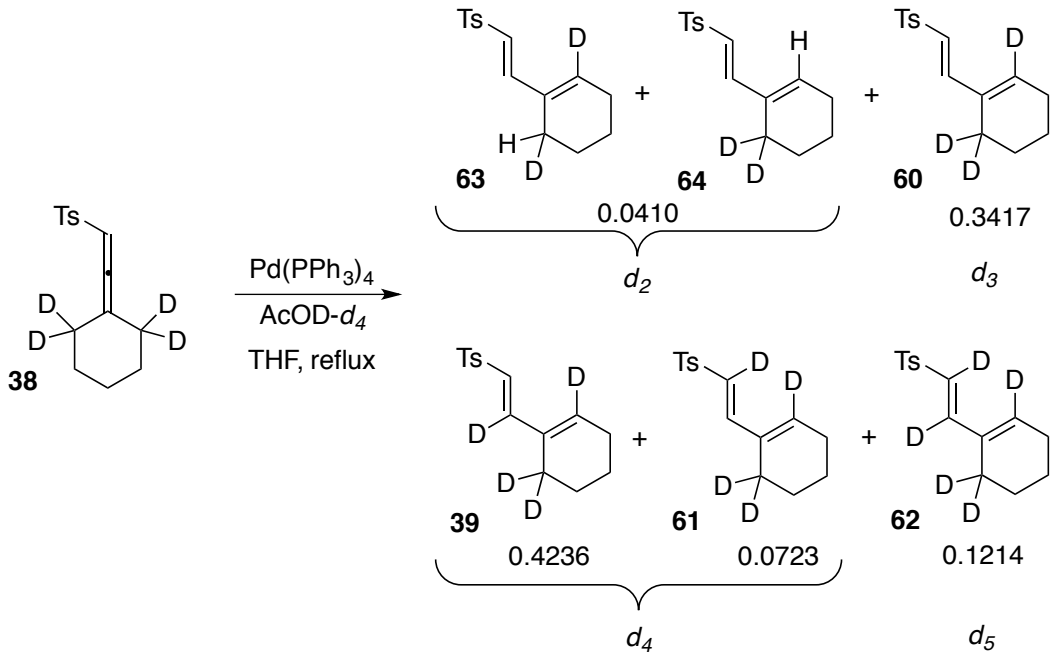
Table 9. Isotopologue contributions to mass ion peaks.

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

Allene **38** was treated under isomerization conditions as shown in Scheme 14. It can clearly be seen in the ^{1}H NMR data in Figure 4 above 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.**

Scheme 14. Diene products from isomerization of allene **38.**



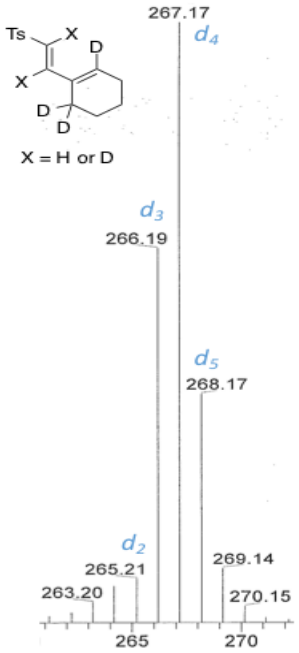


Figure 10. Mass spectrum of deuterated diene mixture.

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 impacted 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 is determined that the allene used in this reaction is a mixture of 0.0329 : 0.1362 : 0.8309 of d_2:d_3:d_4 allenes.

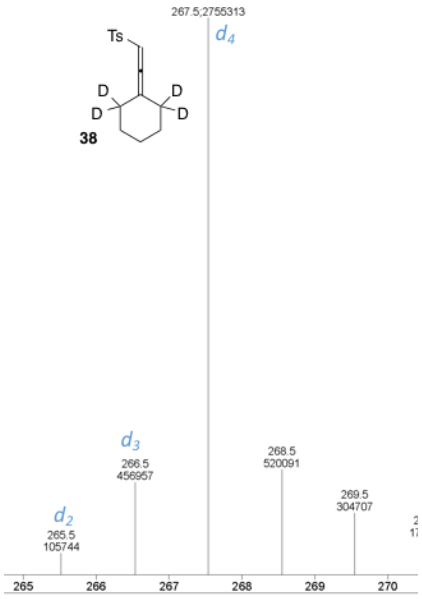


Figure 11. Mass spectrum of allene **38**.

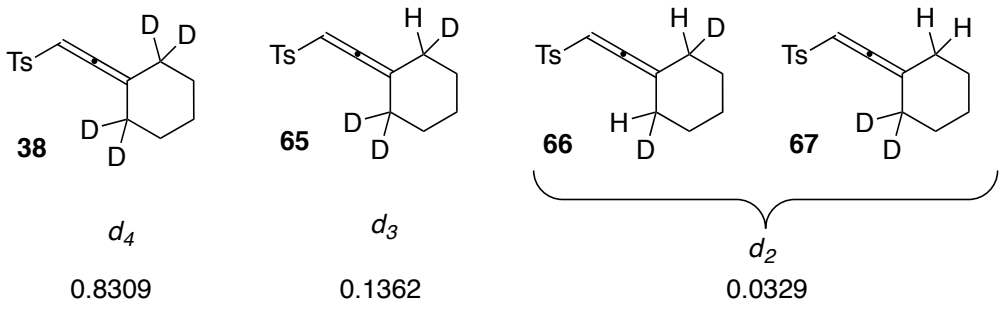


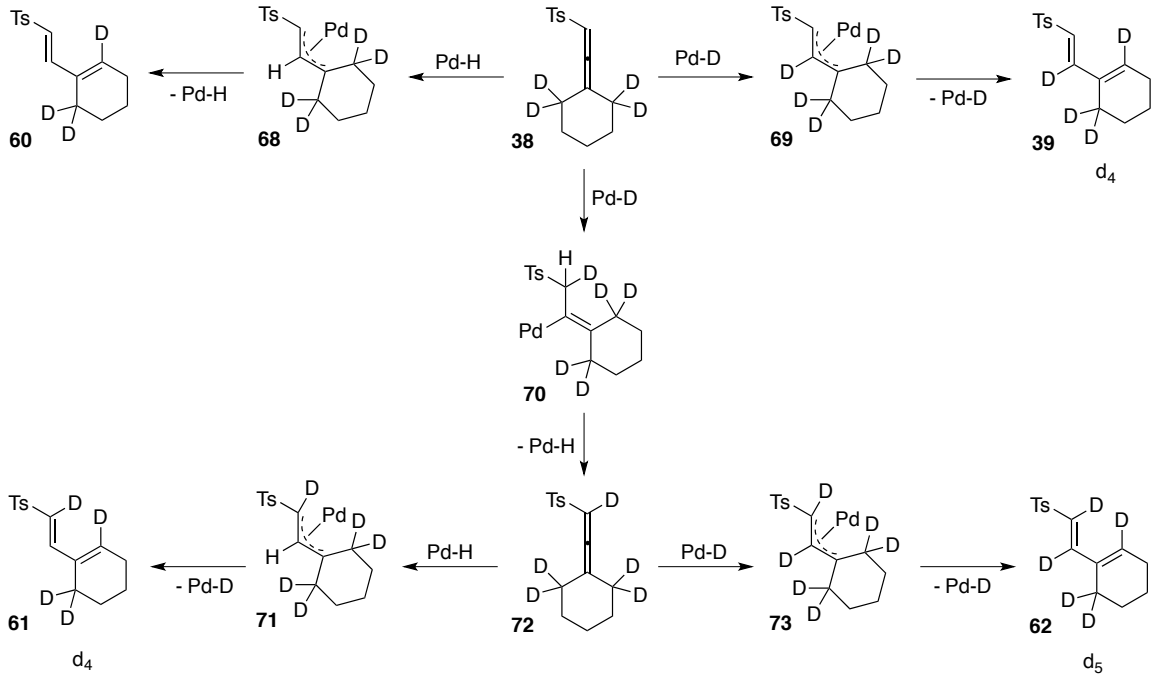
Figure 12. Isotopologues of the deuterated allene starting material

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

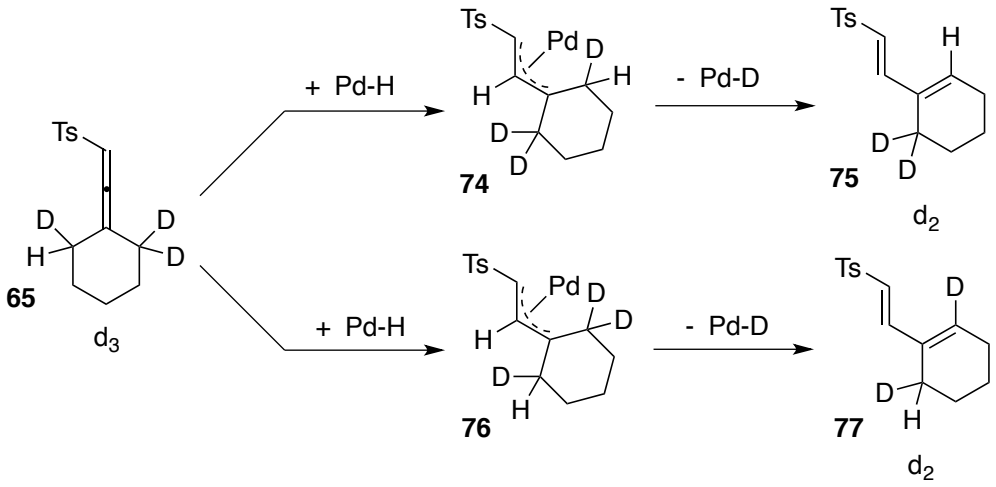
This same process was repeated on two more batches of starting material allenes and the resulting diene product mixtures. The results are consistent in that the starting allenes are generally ~82-85% tetradeuterated and the diene mixtures contain a smaller percentage of d_4 isomers, with formation of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

16), taking into account that the mass spectrum shows that the allene is not fully tetradeuterated and contains some lesser-deuterated analogs.

Scheme 15. Generation of diene isotopologues stemming from **38**.



Scheme 16. Generation of d_2 diene isotopologues stemming from **65**.

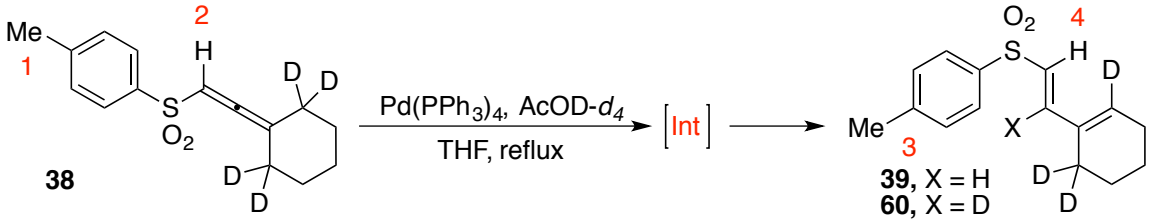


The data above illustrates the ability of a Pd-D to deuteropalladate an allenic sulfone, and that the α-position is interchangeable. In addition, the isotopic mixtures of

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 pipette, and evaporating the solvent at time intervals of every 30 minutes 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, 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.



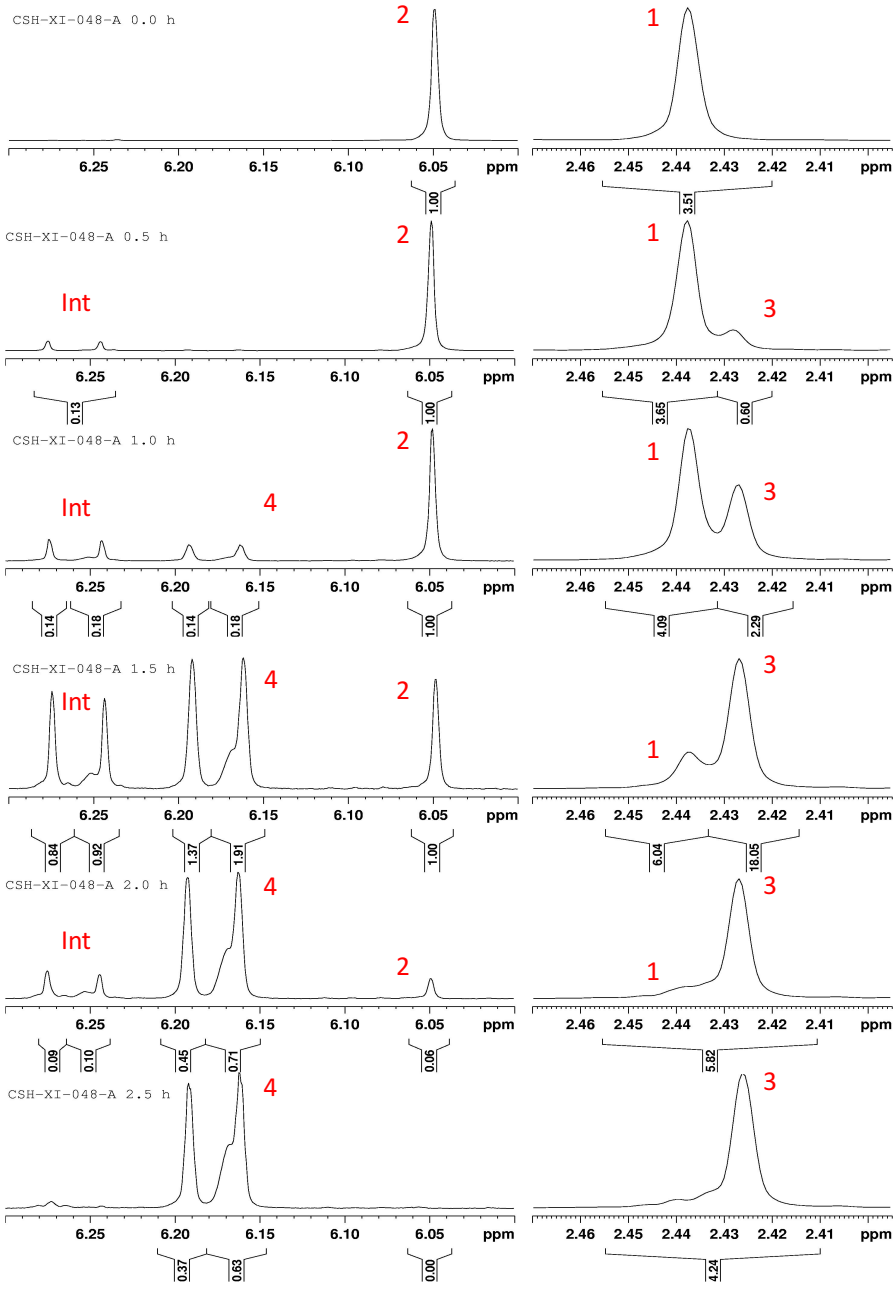
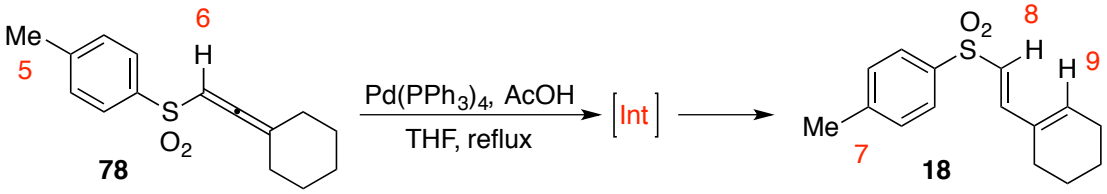


Figure 13. Monitoring the reaction of **38** by ^{1}H NMR.

After observing the formation of an intermediate in the reaction in Figure 8, 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 non-deuterated allene **78** was then monitored by ^{1}H NMR, using non-labeled 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 taken at 15 minute 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 minute timepoint 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).



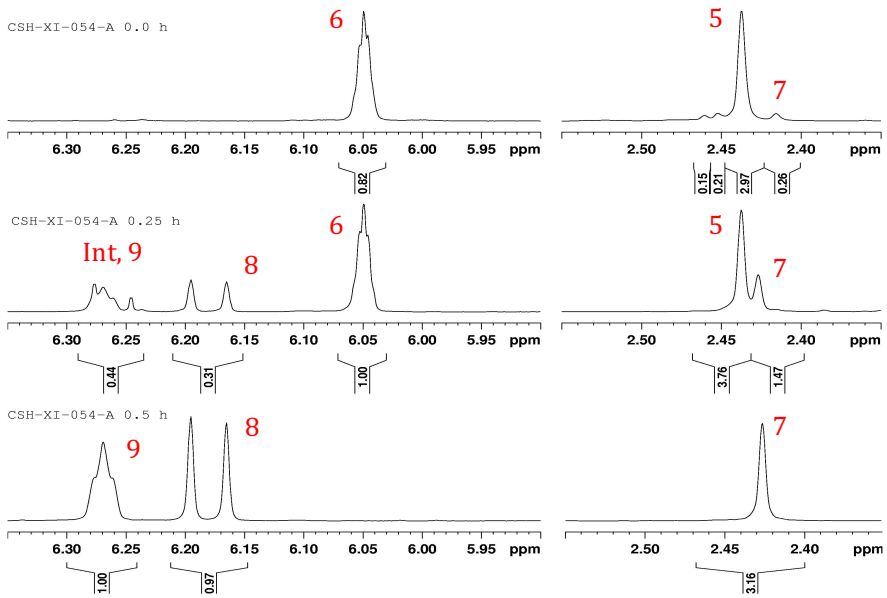
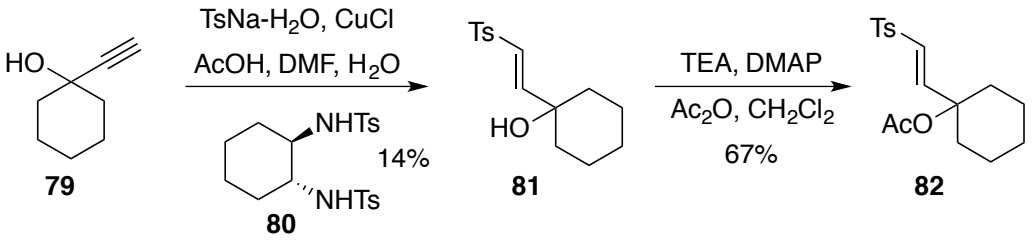


Figure 14. Monitoring the reaction of **77** by ^{1}H NMR.

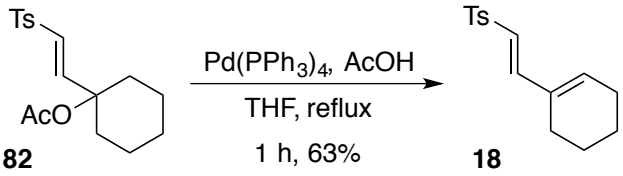
It is known that palladium species can be susceptible to nucleophilic attack, especially by acetate ions.[20] We proposed that the intermediate being formed was the reversible trapping of the palladium species by the acetate ion from acetic acid. To examine this conjecture, the allylic acetate **82** was prepared to compare with the intermediate observed in the reactions monitored by ^{1}H NMR. The allylic acetate **82**, corresponding to the non-deuterated 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.

Scheme 17. Preparation of **82**.



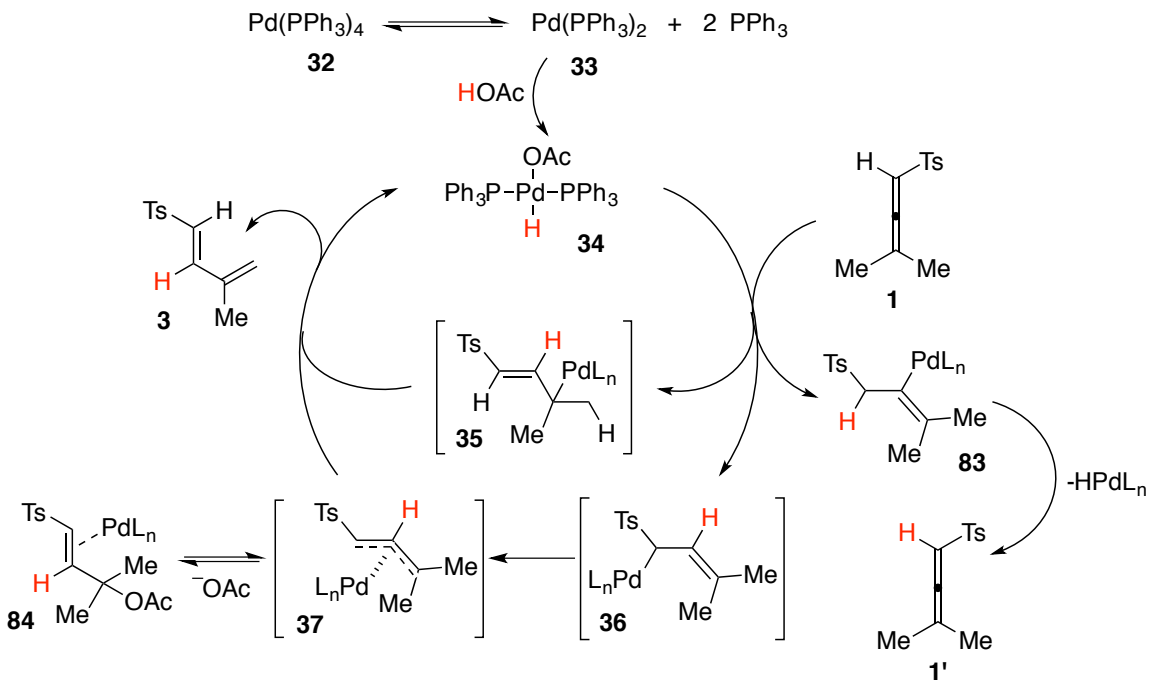
Acetate **82** was then treated under the palladium isomerization reaction conditions to ensure that this species does lead to product formation, and the conversion was completed quickly yielding **18** in 63% yield (Scheme 18), demonstrating that an allylic acetate as an intermediate is feasible. This 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.

Scheme 18. Reaction of **82** to yield **18**.



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).

Scheme 19. Amended mechanism for the palladium-catalyzed isomerization.



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 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 amongst 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.

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 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 MHz or a 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 added to the reaction flask and heated to reflux. Upon complete conversion of starting material by TLC (15% EtOAc:Hexanes) the reaction was cooled to room temperature. Water was added to the reaction flask and the mixture was extracted with CH_2Cl_2 three times. 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:Hexanes) to yield **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):** Product was prepared by a method similar as 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):** Product was prepared by a method similar as 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 affect 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 added to the reaction flask and heated to reflux. Upon complete conversion of starting material by TLC (15% EtOAc:Hexanes) the reaction was cooled to room temperature. Water was added to the reaction flask and the mixture was extracted with CH_2Cl_2 three times. 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:Hexanes) to yield **29** (0.063 g) as an oil in 63% yield.

General Procedure for Isomerization. To an oven-dried round bottom flask with an argon balloon was added the palladium catalyst (10 mol %, unless stated otherwise) and acid cocatalyst (10 mol %, unless stated otherwise) and dry solvent (0.1 M, unless stated otherwise). Then the allenic sulfone was added to the reaction flask and heated to reflux. The reaction was monitored by TLC (15% EtOAc:Hexanes). Either upon reaction completion or prolonged reaction time with no change in TLC, the reaction was cooled to room temperature. Water was added to 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:Hexanes).

Incorporation of deuterium into 1. To an oven-dried round bottom flask was added deuterated acetic acid (0.029 g, 0.450 mmol), $Pd(PPh_3)_4$ (0.15g, 0.135 mmol, 30 mol%) and 5 mL dry THF. Then **1** (0.100 g, 0.450 mmol) in 4 mL dry THF was added. The reaction was heated to reflux under argon and monitored by TLC (15% EtOAc: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 mixture of **3:40:41** 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 hours. The ketone (top layer) was separated from the aqueous layer via separatory funnel and evaluated by ^1H NMR. The process was repeated by adding 5 mL D_2O and 4.3 g of potassium carbonate to the product and refluxing for 24 hours again. The ketone **57** was separated from the aqueous layer, isolated in 78% yield, and evaluated by ^1H NMR.

2,2,6,6-tetradeutero-1-ethynylcyclohexan-1-ol **(58)**[24]**:** In a flame-dried round bottom flask purged with argon is added dry THF (75 mL). The solution is cooled to -78°C in a dry ice-acetone bath and ethynyl magnesium chloride (53.5 mL, 26.74 mmol, 0.5 M in THF) is added. Then a solution of **57** (2.1 g, 20.57 mmol) in 25 mL of dry THF was added dropwise to the reaction flask. The reaction is stirred overnight 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 argon atmosphere, the p-toluenesulfonyl chloride (1.0 eq) was dissolved in CH_2Cl_2 (0.05 M) and triethylamine (1.1 eq) was added. A solution of **58** (1.0 eq) and triphenylphosphine (1.0 eq) in CH_2Cl_2 was added dropwise to the reaction solution over 20 minutes. The reaction was stirred at room temperature and monitored by TLC until consumption of sulfonyl chloride. The reaction mixture was concentrated and a solution of diethyl ether:hexanes (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, washed with diethyl ether, and the filtrate concentrated *in vacuo*. The crude product was purified by column chromatography (3% EtOAc: Hexanes) to yield **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 (0.05M) under an argon atmosphere was added silver hexafluoroantimonate (2 mol%). The reaction was stirred at room 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 yield **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. To a clean oven-dried 25 mL round bottom flask and stir bar was added 2-3 mL D_2O and refluxed for 3 hours. The flask was then cooled to room temperature and the D_2O removed via pipette. Fresh D_2O was then added to the flask and refluxed for an additional 2 hours. 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 hours. 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. To the reaction flask was added 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 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 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:Hexanes).

Monitoring the reaction of 38 by ^{1}H NMR. Acetic acid-d_4 (0.002 g, 0.038 mmol) was added to 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 a bright yellow color, then **38** is added. Immediately, 0.5 mL of the solution is removed via syringe. The flask is heated to reflux. The removed aliquot is filtered through a microscale column made from a glass pipette (filled with a cotton plug, sand, and silica gel). The material is washed through with CH_2Cl_2 (~5 mL). The collected filtrate is concentrated by rotary evaporation and crude ^{1}H NMR taken. The process of removing 0.5 mL aliquots is repeated every 30 minutes. The remaining material after 2.5 hours at reflux is treated with silica gel and concentrated on the rotary evaporator, then purified by column chromatography (5% EtOAc:Hexanes).

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

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 hours. 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: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 stirred at room temperature for 2 days. The reaction was diluted with CH_2Cl_2 after completion by TLC (30% EtOAc: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: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

^{1}H NMR and ^{13}C NMR for all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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References

1. (a) Back, T. G.; Clary, K. N.; Gao, D. *Chem. Rev.* **2010**, *110*, 4498-4553. (b) Back, T. G. *Tetrahedron* **2001**, *57*, 5263-5301. (c) Braverman, S. *Phosphorus Sulfur* **1985**, *23*, 297-326.
2. Padwa, A.; Ni, Z.; Watterson, S. H. *Pure Appl. Chem.* **1996**, *68*, 831-836.
3. (a) Martinelli, F.; Palmieri, A.; Petrini, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2011**, *186*, 1032-1045. (b) El-Awa, A.; Noshi, M.N.; Mollat Du Jourdin, X.; Fuchs, P.L. *Chem. Rev.* **2009**, *109*, 2315-2349. (c) Alonso, D.A.; Najera, C. *Org. React.* **2008**, *72*, 367-656. (d) Trost, B.M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107-124. (e) Najera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547-10658.
4. (a) Hampton, C. S.; Harmata, M. *Org. Lett.* **2014**, *16*, 1256−1259. (b) Hampton, C.S.; Harmata, M. *J. Org. Chem.* **2015**, *80*, 12151-12158. (c) Tata, R.R.; Hampton, C.S.; Altenhofer, E.F.; Topinka, M.; Ying, W.; Gao, X.; Harmata, M. *Chem.- Eur. J.* **2014**, *20*, 13547-13550. (d) Tata, R.R.; Harmata, M. *J. Org. Chem.* **2015**, *80*, 6839-6845.
5. (a) Ma, D.; Lin, Y.; Lu, X.; Yu, Y. *Tetrahedron Lett.* **1988**, *29*, 1045−1048. (b) Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301−2303.
6. Inoue, Y.; Imaizumi, S. *J. Mol. Catal.* **1988**, *49*, L19-L21.
7. Ma, D.; Yu, Y.; Lu, X. *J. Org. Chem.* **1989**, *54*, 1105-1109.

8. Hirai, K.; Suzuki, H.; Morooka, Y.; Ikawa, T. *Tetrahedron Lett.* **1980**, *21*, 3413-3416.

9. Ma, C.; Lu, X.; Ma, Y. *Main Group Met. Chem.* **1995**, *18*, 391−397.

10. (a) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933−7935. (b) Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659−2660.

11. Ma, C. L.; Lu, X. Y.; Ma, Y. X. *Chin. Chem. Lett.* **1995**, *6*, 747−750.

12. Lu, X.; Ma, D. *Pure Appl. Chem.* **1990**, *62,* 723−730.

13. Tolman, C. A.; Seidel, W. C.; Gerlach, D. H. *J. Amer. Chem. Soc.* **1972,** *94*, 2669-2676.

14. (a) Davies, W. C.; Lewis, W. P. G. *J. Chem. Soc.* **1934**, 1599-1604. (b) Tolman, C. A. *Chem. Rev.* **1977,** *77*, 313-348.

15. Romeo, R.; Plutino, M. R.; Monsu, S. L.; Stoccoro, S. *Inorg. Chim. Acta* **1997,** *265*, 225-233.

16. Trost, B.M. *Chem.- Eur. J.* **1998**, *4*, 2405-2412.

17. (a) Cruikshank, B. I.; Davies, N. R. *Aust. J. Chem.* **1973,** *26*, 1935-1947. (b) Cruikshank, B. I.; Davies, N. R. *Aust. J. Chem.* **1973,** *26*, 2635-2648.

18. (a) Harmata, M.; Huang, C. *Adv. Synth. Cat.* **2008**, *350*, 972-974. (b) Harmata, M.; Cai, Z.; Huang, M. *Org. Synth.* **2011**, *88*, 309-316.

19. It is important to note that sensitivity and detection limits of the instrument must be taken into account. As a result, there is the possibility that the spectral data may not match theoretical calculations exactly.

20. (a) Harrod, J. F.; Chalk, A. J. *J. Am. Chem. Soc.* **1964,** *86* (9), 1776-9. (b) Stern, E. W.; Spector, M. L. *Proc. Chem. Soc., London* **1961**, 370.

21. Taniguchi, N. *Synlett* **2012,** *23*, 1245-1249.

22. Grushin, V. V. *Chem. Rev.* **1996,** *96*, 2011-2033.

23. Ellis, P.D.; Maciel, G.E. *J. Am. Chem. Soc.* **1970**, *92*, 5829-5833.

24. Jadhav, A.M.; Gawade, S.A.; Vasu, D.; Dateer, R.B.; Liu, R.-S. *Chem.-Eur. J.* **2014**, *20*, 1813-1817.

25. Stones, G.; Tripoli, R.; McDavid, C. L.; Roux-Duplatre, K.; Kennedy, A. R.; Sherrington, D. C.; Gibson, C. L. *Org. Biomol. Chem.* **2008,** *6*, 374-84.