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Regiodivergent Synthesis of 1- and 2-Arylsulfonyl 1,3-Dienes

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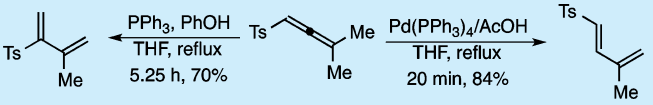
Supporting Information

ABSTRACT: In the course of a study of the alkoxyallylation of allenic sulfones through the use of π-allylpalladium chemistry, we discovered an isomerization of allenic sulfones to arylsulfonyl 1,3-dienes. Under conditions of palladium catalysis in the presence of acids such as acetic acid, allenic sulfones are converted to 1-arylsulfonyl 1,3-dienes. On the other hand, nucleophilic catalysis using triphenylphosphine in the presence of a proton shuttle yields 2-arylsulfonyl 1,3-dienes. Thus, either regioisomer of the arylsulfonyl diene can be prepared at will based on changes in reaction conditions.

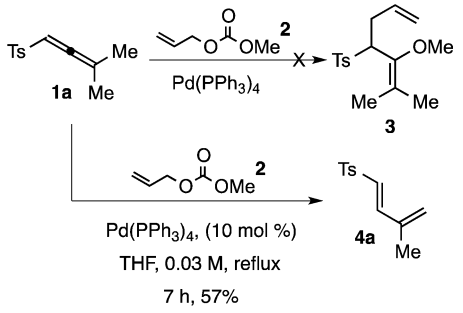


Allenic sulfones are powerful reagents in organic synthesis.[1] They participate in many types of processes, including cycloaddition and cyclization reactions.[2] The sulfone group serves to activate the allene as an electron-withdrawing group, but it can be easily removed by various desulfonylation methods.[3]

We have an ongoing interest in the development of (4 + 3)-cycloaddition reactions,[4] including intramolecular cycloadditions of alkoxyallylic sulfones[5] or (trimethylsilyl)methyl allylic sulfones.[6] In the former case, a key process in the synthesis of the starting material is the addition of an alkoxide to an allenic sulfone.[7] We wondered whether we could perform such a reaction coupled to an alkylation in order to facilitate the synthesis of substrates for (4 + 3)-cycloaddition reactions. To that end, we treated a mixture allenic sulfone **1a** and allylic carbonate **2** with $Pd(PPh_3)_4$ in anticipation of forming **3** via alkoxide addition to the allene followed by alkylation with the π-allyl palladium complex formed during the course of the reaction.[8]

In the event, the reaction of **1a** and **2** in the presence of 10 mol % of tetrakis(triphenylphosphine)palladium in refluxing THF afforded not **3** but a 57% yield of **4a** (Scheme 1). This appeared to be a new reaction of allenic sulfones, which we subsequently decided to pursue.

Scheme 1. Attempted Formation of 3 via Nucleophilic Addition/Allylation



Scheme 2. Nucleophilic Catalysis of Allene Ester Isomerization

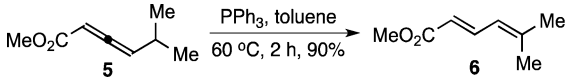
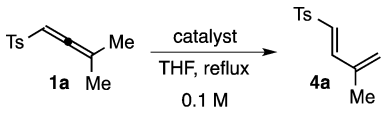


Table 1. Examination of Catalyst Variation for the Synthesis of Diene 4a



entry	catalyst[a]	time	yield (%)
1	$Pd_2(dba)_3$	32 h	6[b]
2	$Pd(OAc)_2$	20 h	5[c]
3	$Pd(OAc)_2/PPh_3$	25 min	81
4	$Pd(PPh_3)_4$	7 h	57
5	$Pd(PPh_3)_4$/AcOH	20 min	84

[a]10 mol % of catalyst (and cocatalyst where appropriate) were used. [b]81% recovered **1a**. [c]66% recovered **1a**.

The formation of dienes through metal or nucleophilic catalysis is well established in the rearrangement of alkynes substituted with carbonyl groups.[9]

One of the few reported isomerizations of an allenic system to a conjugated diene was demonstrated by Trost under phosphine catalysis (Scheme 2).[9c] The paucity of literature on allene isomerization is most likely due to the fact that alkynes are generally easier to synthesize than allenes.[10,11]

We began our studies by examining a small selection of catalysts using **1a** as a substrate. The results are shown in Table 1. The use of palladium catalysts such as $Pd(OAc)_2$ and $Pd_2(dba)_3$ alone resulted in recovered starting material with only trace amounts of isomerized product **4a** being observed. The use of $Pd(PPh_3)_4$ alone provided the isomerized product, albeit in modest yield (57%). When triphenylphosphine was

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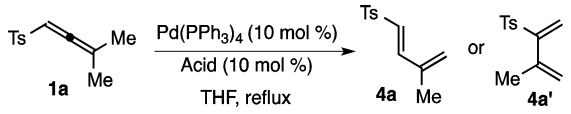
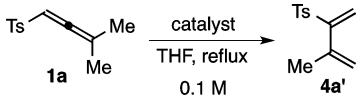
Table 2. Acid Effect on Product Formation



entry	acid	pK_a [a]	time	4a	4a′
1	*p*-TolSO$_3$H	−2.3	5 min	87	
2	CH$_3$CO$_2$H	4.76	20 min	84	
3	Me$_3$CCO$_2$H	5.03	25 min	79	
4	4-nitrophenol	7.15	8 h	76	
5	3-chlorophenol	9.02	24 h	60	
6	2-naphthol	9.51	24 h		42
7	phenol	9.98	2 h		74
8	2,6-diphenylphenol	10.01	2.6 h		53
9	BHT[b]	12.23	23 h		54

[a] pK_a in aqueous solution. [b] BHT = 2,6-di-*tert*-butyl-4-methylphenol.

Table 3. Catalyst Conditions for Isomerization of 1a to 4a′



entry	catalyst system[a]		time	yield of 1a (%)	yield of 4a′ (%)
1	PPh$_3$		22 h	50	
2	PPh$_3$	AcOH	5 h		31
3	PPh$_3$	PhOH	5.25 h		70
4	PPh$_3$	BHT[b]	4 h		54
5	PhSO$_2$Na		32 h	35	
6	TsNa·H$_2$O	BHT[b]	36 h		60
7		AcOH	20 h	48	
8		BHT[b]	20 h	51	

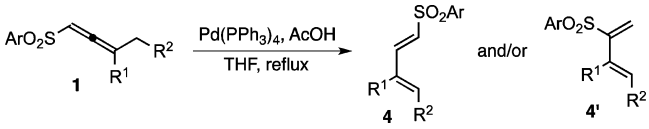
[a] 20 mol % of catalyst (and cocatalyst where appropriate) were used. [b] BHT = 2,6-di-*tert*-butyl-4-methylphenol.

used in combination with Pd(OAc)$_2$, the reaction proceeded both relatively quickly and in high yield. This suggested that the addition of acetic acid to the Pd(PPh$_3$)$_4$ catalyst would increase the rate of the reaction. Indeed, as mentioned by Trost and Schmidt in their acetylene isomerization work,[9f] the addition of a weak acid to the reaction when a Pd(0) catalyst was used greatly improved both the yield and reaction rate (Table 1, entry 5).

To determine the effect of the acidity of cocatalysts on the reaction, we varied the pK_a of the acid used to accelerate the reaction. Some of these results are shown in Table 2. The reaction afforded **4a** in the presence of *p*-toluenesulfonic acid monohydrate in 87% yield, and we were able to demonstrate that the reaction did not proceed in the absence of palladium; i.e., it is not acid-catalyzed. Acids similar to acetic acid also performed well (Table 2, entry 2).

Since Rychnovsky reported that phenol was a good cocatalyst for the phosphine-catalyzed isomerization of alkynones,[12] we tried phenol as the cocatalyst in our palladium-catalyzed isomerization. Instead of **4a**, we isolated a new product, identified as the 2-arylsulfonyl diene **4a′** (Table 2, entry 7). As a result, we began studying the effects of phenols on the product formation as well (Table 2, entries 4−9). The results seem to show that at a pK_a of ∼9.0−9.5 (aqueous pK_a values) there is a change in product formation and consequently a change in the mechanism of the process.

Table 4. Isomerization of Allenic Sulfones To Form 1-Arylsulfonyl Dienes[a]



entry	substrate	Ar	R^1	R^2	time	product	yield of 4 (%)
1	**1a**	*p*-Tol	Me	H	20 min	**4a**	84
2	**1b**	Ph	Me	H	50 min	**4b**	75
3	**1c**	2-naphthyl	Me	H	45 min	**4c**	77
4	**1d**	mesityl	Me	H	4.3 h	**4d**	84
5	**1e**	trisyl	Me	H	3.6 h	**4e**	81
6	**1f**	4-(MeO)C$_6$H$_4$	Me	H	35 min	**4f**	78
7	**1g**	2-Thienyl	Me	H	2 h	**4g**	68
8	**1h**	4-(CF$_3$)C$_6$H$_4$	Me	H	20 min	*b*	*b*
9	**1i**	3,5-bis(CF$_3$)C$_6$H$_3$	Me	H	25 min	*c*	*c*
10	**1j**	*p*-Tol	−(CH$_2$)$_3$−		2.5 h	**4j**	74
11	**1k**	*p*-Tol	−(CH$_2$)$_4$−		5 h	**4k**	97
12	**1l**	Ph	−(CH$_2$)$_4$−		5 h	**4l**	93
13	**1m**	2-thienyl	−(CH$_2$)$_4$−		9 h[d]	**4m**	75
14	**1n**	3,5-bis(CF$_3$)C$_6$H$_3$	−CH$_2$CH$_2$-C(Me)$_2$C-H$_2$−		40 min	*e*	*e*
15	**1o**	*p*-Tol	H	Et	2 h	**4o**	45
16	**1p**	*p*-Tol	H	*i*-Pr	2 h	**4p**	63
17	**1q**	*p*-Tol	H	Ph	2 h	**4q**	70
18	**1r**	*p*-Tol	H	*f*	2 h	**4r**	88

[a] The reactions were conducted at a concentration of 0.1 M using 10 mol % of catalyst and cocatalyst. [b] **4h′** was isolated in a 56% yield. [c] **4i′** was isolated in a 61% yield. [d] Identical R$_f$ values for **1m** and **4m** led to a longer reaction time, as we were not certain when the reaction was complete. [e] The product was isolated as a 1:4 mixture (NMR) of **4n**:**4n′** in 54% yield. [f] R^{2}CH$_2$− = cyclohexyl.

Mechanistic considerations led us to realize that palladium was not necessary for the formation of **4a′**, and several experiments were conducted to examine this idea. The results are summarized in Table 3. Triphenylphosphine alone in refluxing THF consumed **1a** to the extent of 50%, but no diene of any type was produced (Table 3, entry 1). Triphenylphosphine and acetic acid afforded a low yield of **4a′** (Table 3, entry 2). As expected, the presence of phenol or BHT in conjunction with triphenylphosphine resulted in good yields of **4a′**, with phenol being superior (Table 3, entries 3 and 4). We hypothesized that during the course of the reaction arylsulfinate ions were being produced and were actually responsible for the formation of **4a′**.[13] Interestingly, when sodium benzenesulfinate was used as a catalyst, only a low yield of starting material could be isolated from the reaction (Table 3, entry 5). However, when sodium *p*-toluenesulfinate hydrate in combination with BHT was used as the catalyst, diene **4a′** was obtained in 60% yield (Table 3, entry 6). Neither acetic acid alone nor BHT alone afforded any diene product (Table 3, entries 7 and 8).

With this information in hand, we set out to explore the scope and limitations of both the palladium-catalyzed and phosphine-catalyzed isomerizations. The results are summarized in Tables 4 and 5.

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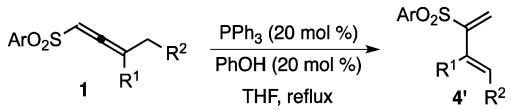
Table 5. Formation of 2-Arylsulfonyl Dienes[a]



entry	substrate	time	product	yield of 4′ (%)
1	**1a**	5.25 h	**4a′**	70
2	**1b**	8.5 h	**4b′**	42
3	**1c**	4 h	**4c′**	79
4	**1d**	6 h	**4d′**	52
5	**1e**	16 h	*b*	*b*
6	**1f**	2.75 h	**4f′**	64
7	**1g**	35 min	**4g′**	71
8	**1h**	15 min	**4h′**	68
9	**1i**	45 min	**4i′**	63
10	**1j**	30 min	**4j′**	57
11	**1k**	2 h	**4k′**	40[c]
12	**1l**	4 h	**4l′**	[c]
13	**1m**	9 h[d]	**4m′**	52[c]

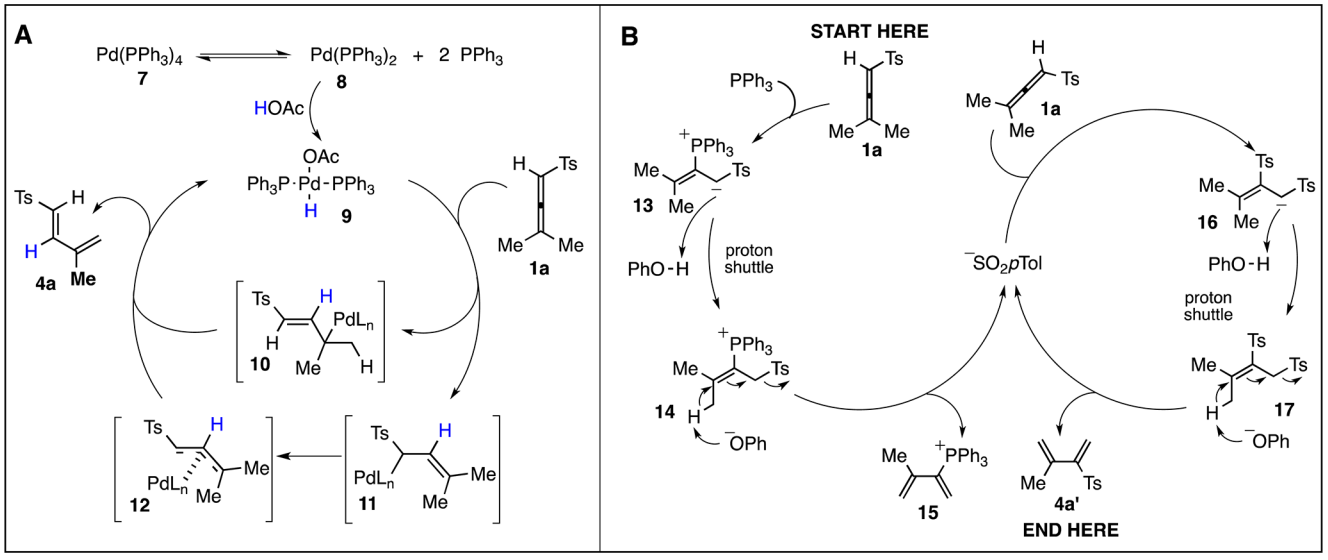
[a]The reactions were conducted at a concentration of 0.1 M using 20 mol % of catalyst and cocatalyst. [b]41% of **1e** was recovered. [c]Expected product as well as a byproduct from 1,4-addition of phenol to the allenic sulfone were observed. [d]Identical R_f values for **1m** and **4m′** led to longer reaction time as we were not certain when the reaction was complete.

For the palladium-catalyzed process, we used a 10 mol % loading of $Pd(PPh_3)_4$ along with an equimolar amount (with respect to Pd) of AcOH. The reactions were conducted in refluxing THF at a concentration of 0.1 M with respect to the substrate and were monitored by TLC at regular intervals. We first examined the effect of the aryl group associated with the sulfone functional group on the course of the reaction. For simple, unhindered groups such as phenyl, *p*-methylphenyl, and 2-naphthyl, the reaction was complete in less than 1 h and furnished the corresponding 1-arylsulfonyl-substituted dienes in very good yields (Table 4, entries 1−3). As the size of the aryl group increased to mesityl and trisyl, the reaction proceeded more slowly but still afforded excellent yields of products (Table 4, entries 4 and 5). Electronic effects based on the aryl group were not expected to be too dramatic. Thus, the *p*-methoxybenzenesulfonyl system reacted essentially in the same fashion as the simple phenyl system (Table 4, entry 6). Interestingly, the thiophene-2-yl system required more time to go to completion but still delivered a good yield of diene (Table 4, entry 7). As the aryl ring became more electron-deficient, the reaction began to change course. For the dimethyl-substituted allenes **1h** and **1i**, the reaction afforded only **4h′** in 56% yield and **4i′** in 61% yield, respectively (Table 4, entries 8 and 9). With the allene **1n**, the reaction afforded a 54% yield of an inseparable mixture of the expected product **4n** as well as **4n′** in a 1:4 ratio (Table 4, entry 14). Since $Pd(PPh_3)_4$ liberates free PPh_3 in solution,[14] it is likely that in these latter cases the increased electrophilicity of the allene dominates the reaction and nucleophilic attack on the allene proceeds more quickly than the Pd-catalyzed process, leading to increasing or complete formation of the 2-arylsulfonyl dienes. Finally, we have conducted a brief study of the effect of varying substitution on the allene on the process. Five and six-membered rings led to dienes uneventfully and in good yield (Table 4, entries 10−12).

γ-Monosubstituted allenes also isomerized readily to the corresponding 1-arylsulfonyl dienes in fair yield (Table 4, entries 15−18).

The results for the phosphine-catalyzed reactions are summarized in Table 5. In the phosphine/phenol-catalyzed reaction, electron-withdrawing groups on the aromatic ring of the sulfonyl functional groups led to rapid isomerization to the corresponding 2-substituted sulfonyl diene, possibly due to the better leaving group ability of the sulfinate anions involved (Table 5, entries 8 and 9). Allenes bearing relatively electron-rich groups such as the thiophene or the *p*-methoxyphenyl rearrange at reaction rates that are qualitatively rather fast as well, perhaps due to increased nucleophilicity of the sulfinate anions involved (Table 5, entries 6 and 7). Compounds with sulfonyl groups with weakly electron-rich substituents (Table 5, entries 1, 3, and 4) were followed by compounds such as the phenylsulfonyl-substituted **1b**, which took the longest time to react among those allenes whose sulfonyl substituents were not sterically encumbering (Table 5, entries 2 and 5).

Scheme 3. Mechanistic Proposals for the Formation of 1- and 2-Arylsulfonyldienes from Allenes



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The data obtained thus far in conjunction with mechanistic hypotheses put forth in the literature on related processes suggest a mechanism for the formation of 1-arylsulfonyl dienes such as **4a** as depicted in Scheme 3, box A. Thus, oxidative addition of a coordinatively unsaturated Pd(0) species (**8**) to acetic acid produces the palladium hydride intermediate **9**. This hydropalladates **1a** to produce **10** or **11**. Subsequent β-hydride elimination from **10** or the π-allylpalladium intermediate **12** affords **4a** and regenerates **9**.

The formation of **4a′** appears to be more complex. We postulate that nucleophilic addition of triphenylphosphine to **1a** produces **13**, which deprotonates phenol to produce **14** (Scheme 3, box B). The resultant phosphonium salt is deprotonated by the resulting phenoxide, eliminating a sulfinate anion and affording the phosphonium salt **15**. This step is actually critical in generating the small amounts of sulfinate ion necessary to produce **4a′**. Thus, nucleophilic addition of arylsulfinate anion to **1a** produces **16** and once again phenol serves as a proton shuttle, ultimately regenerating sulfinate anion and producing **4a′**. Efforts to lend support to these mechanistic proposals are underway.

In summary, we have developed methods for the selective conversion of readily accessible arylsulfonyl allenes[15] to either 1-arylsulfonyl- or 2-arylsulfonyl dienes. Further studies of these isomerization processes, their scope and mechanism, and the application of the products to synthetic problems are underway, and results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and copies of ^{1}H and ^{13}C NMR spectra for new 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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