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Palladium-Catalyzed Regio- and Enantioselective Hydrosulfonylation of 1,3-Dienes with Sulfinic Acids: Scope, Mechanism, and Origin of Selectivity

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ABSTRACT: Chiral sulfones are important structural motifs in organic synthesis owing to their widespread use in pharmaceutical chemistry. In particular, chiral allylic sulfones have drawn particular interest because of their synthetic utility. However, enantioselective synthesis of 1,3-disubstituted unsymmetrical chiral allylic sulfones remains a challenge. In this article, we report a protocol for (*R*)-DTBM-Segphos/Pd-catalyzed regio- and enantioselective hydrosulfonylation of 1,3-dienes with sulfinic acids, which provides atom- and step-economical access to 1,3-disubstituted chiral allylic sulfones. The reaction occurs under mild conditions and has a broad substrate scope. Combined experimental and computational studies suggest that the reaction is initiated by a ligand-to-ligand hydrogen transfer followed by a C–S bond reductive elimination via a six-membered transition state. Steric repulsion between the olefinic C–H of the substrate and the *tert*-butyl group of (*R*)-DTBM-Segphos was found to be a key factor in the enantiocontrol.

1. INTRODUCTION

Chiral sulfones are present in many drugs and also exist in some biologically active natural products (Figure 1).[1] Because the sulfone group is bioisosteric with the carbonyl group, chiral sulfones have been used extensively in modern pharmaceutical chemistry, and the ability of sulfone groups to form strong hydrogen bonds with biological targets makes them useful for improving drug potency and efficacy.[2] Optical pure allylic sulfones are among the most important chiral sulfone building blocks because the alkene can be elaborated in many ways. Therefore, the development of methods for the construction of allylic sulfones, coupled with subsequent transformation of the alkene, would afford access to various functionalized chiral sulfones.[3]

One of the most widely used methods for preparing chiral allylic sulfones is the transition-metal-catalyzed enantioselective allylic substitution (the Tsuji–Trost reaction; Scheme 1a).[4] However, this method affords allylic sulfones with a terminal olefin moiety (γ-substituent = H) or symmetric sulfones (α-substituent = γ-substituent).[5] Chiral allylic sulfones can also be synthesized by asymmetric hydrothiolation of allenes or 1,3-dienes followed by oxidation of the resulting thioethers to sulfones (Scheme 1b).[6] Although this reaction shows good regio- and enantioselectivities, selective access to 1,3-unsymmetrical chiral allylic sulfones via this route has also not been achieved. Moreover, its practicality is limited by the need to use odorous sulfur reagents and strong oxidants.

Hydrosulfonylation of unsaturated C–C bonds with sulfinic acids is the most atom- and step-economical way to construct sulfone subunits. Recently, hydrosulfonylation

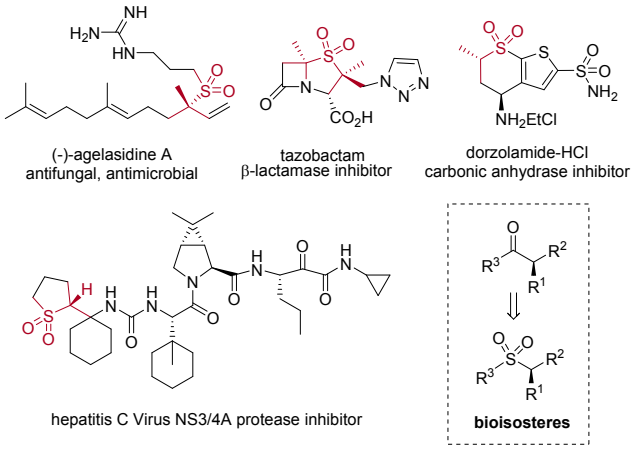
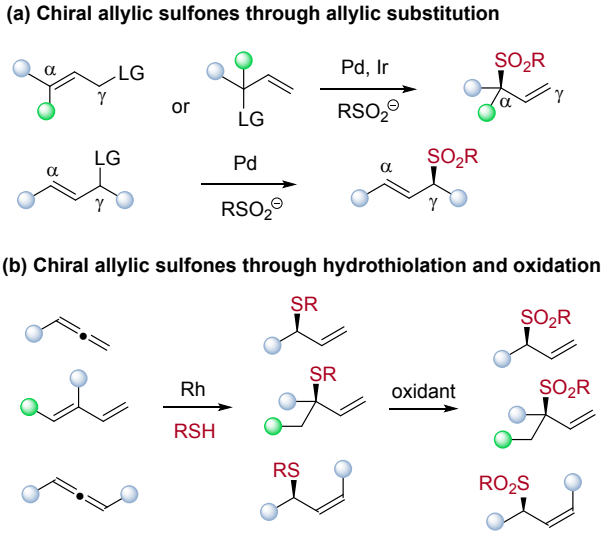


Figure 1. Natural products and drugs containing chiral sulfone motifs.

of alkenes and allenes via radical addition[7] reactions has been extensively studied. However, enantioselective versions of these reactions have not been developed, largely because of the difficulty to control the stereochemistry in a radical pathway.[8] Herein, we report a (*R*)-DTBM-Segphos/Pd-catalyzed enantioselective hydrosulfonylation reaction of 1,3-dienes[9–11] with sulfinic acids to afford 1,3-unsymmetrical chiral allylic sulfones which are otherwise challenging to synthesize (Scheme 1c). The reaction occurs under mild conditions and has a wide substrate scope. Combined experimental and computational studies suggested that the reaction is initiated by a ligand-to-ligand hydrogen transfer (LLHT),[12]

which is followed by a C–S bond reductive elimination via a six-membered transition state. The LLHT is the enantiodetermining step, and the hydrogen is transferred to the same prochiral face of the (*E,E*)- and the (*E,Z*)-1,3-dienes, allowing stereoconvergent hydrosulfonylation of 1,3-dienes. Notably, this discovery represents the first example of palladium involved LLHT process.[12e]

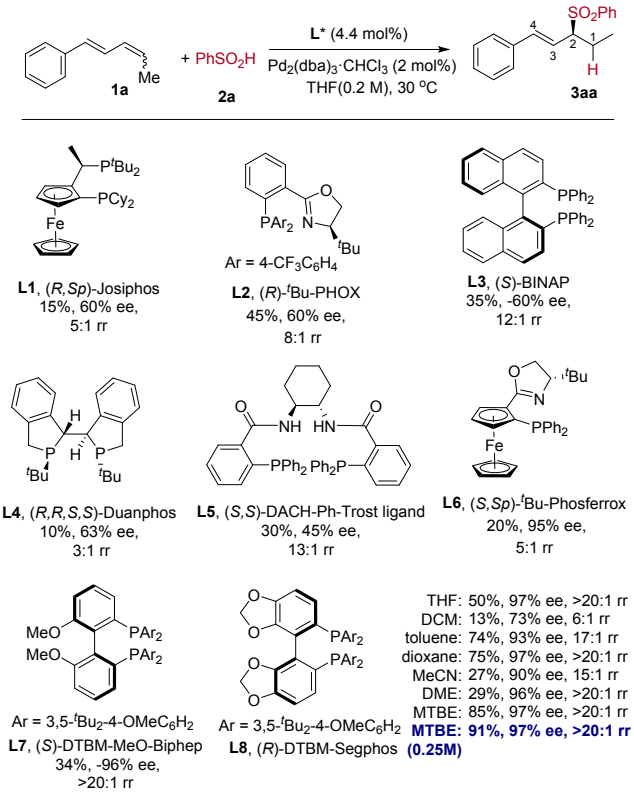
Scheme 1. Strategies for Synthesis of Chiral Allylic Sulfones



2. RESULTS AND DISCUSSION

2.1. Reaction Development. We began our studies by carrying out reactions of 1,3-diene **1a** with phenyl sulfinic acid (**2a**) with catalysis by $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence of various chiral ligands **L** (Table 1). Josiphos (**L1**), *t*-Bu-PHOX (**L2**), BINAP (**L3**), Duanphos (**L4**), and DACH-Ph-Trost ligand (**L5**) were found to give moderate yields of the desired product (**3aa**). However, poor enantioselectivities and regioselectivities were obtained with these ligands. The reaction with *t*-Bu-Phosferrox (**L6**) as a ligand gave **3aa** with 95% ee; but the yield was only 20%, and the 1,2-/4,3-regioselectivity ratio was 5:1. In contrast, the use of sterically demanding bisphosphine ligands DTBM-MeO-Biphep (**L7**) and DTBM-Segphos (**L8**) provided excellent enantio- and regiocontrol, although the yields of **3aa** were somewhat low. Using **L8** as the ligand, we tested various solvents and found that methyl *tert*-butyl ether was the best reaction medium (85% yield, 97% ee). Increasing the concentration of **1a** to 0.25 M increased the yield of **3aa** to 91% without affecting the enantio- and regioselectivity (97% ee, >20:1 rr).

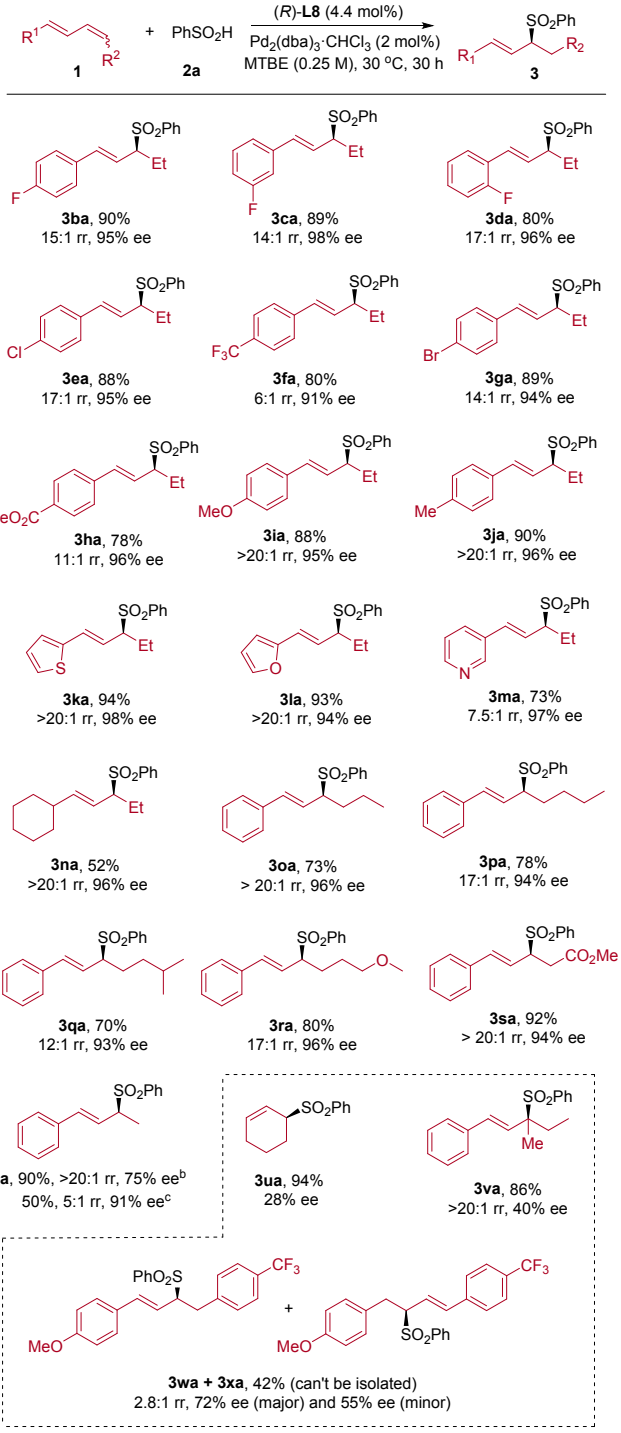
Table 1. Reaction Development[a]



[a]Reaction conditions: **1a** (2.9:1 *EZ*/*EE*, 0.1 mmol), **2a** (0.15 mmol), 30 °C, 48 h. Isolated yields are reported. The regioisomeric ratios (rr) was referred to 1,2-hydrosulfonylation/4,3-hydrosulfonylation, which were determined by ^{1}H NMR analysis of crude reaction mixtures. The enantiomeric excess (ee) values were determined by HPLC on a chiral stationary phase.

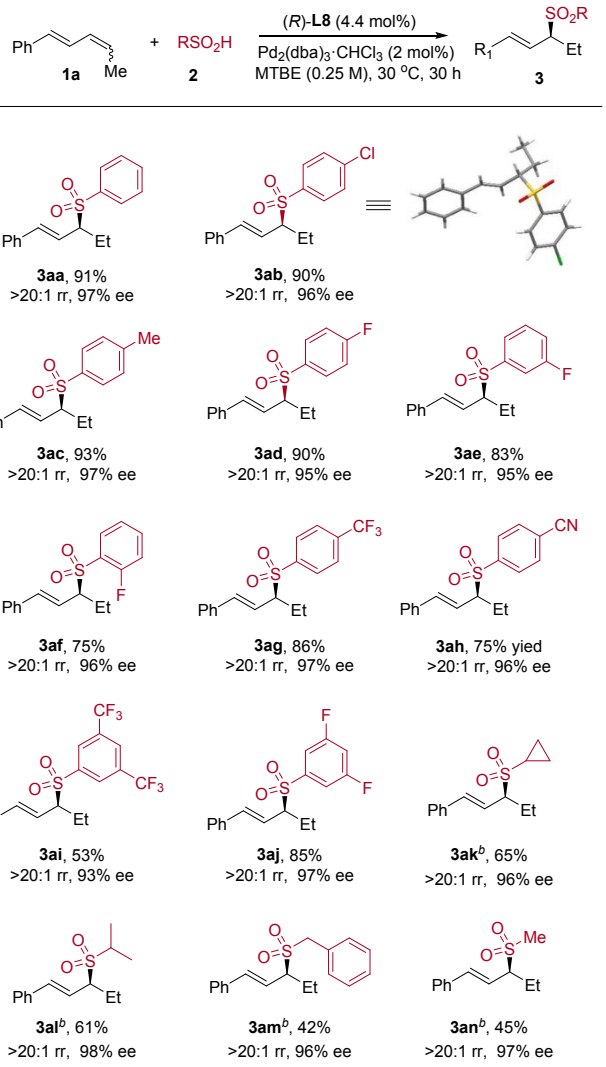
2.2. Substrate Scope. Having developed an effective catalyst system for this regio- and enantioselective hydrosulfonylation reaction, we investigated its substrate scope by carrying out reactions of **2a** with various 1,3-dienes **1** (Table 2). We began with substrates for which R^1 was a substituted phenyl group and R^2 was methyl. Although good yields and enantioselectivities were observed for substrates with an electron-withdrawing fluorine atom (**3ba**, **3ca** and **3da**), chlorine atom (**3ea**), CF_3 group (**3fa**), bromine atom (**3ga**) or CO_2Me group (**3ha**), the regioselectivities were slightly lower than those observed for **1a**. In contrast, electron-donating MeO (**3ia**) and Me (**3ja**) groups were well-tolerated. 1,3-Dienes with a thiophene or furan ring as R^1 gave the corresponding hydrosulfonylation products (**3ka** and **3la**) in 94% and 93% yields, respectively. Pyridine derived 1,3-diene was compatible, affording **3ma** in 73% yield with 97% ee, albeit with a moderate regioselectivity. We reasoned that electron-deficient arenes (**3fa**, **3ha** and **3ma**) might destabilize the Pd-π-allyl species involved in the 1,2-hydrosulfonylation, but they were with little influence on the stability of the Pd-π-allyl species involved in the 4,3-hydrosulfonylation pathway. Therefore, for these substrates, the regioselectivities dropped. When a substrate with two different alkyl groups (R^1 = cyclohexyl, R^2 =

Table 2. Scope of the Reaction with Respect to the 1,3-diene[a]



[a]See SI for details. Isolated yields are reported. The rr values were determined by ^{1}H NMR analysis of crude reaction mixtures. The ee values were determined by HPLC on a chiral stationary phase. [b]The reaction time was 2h. [c]**L6** was used as the ligand, and the reaction was carried out at 5 °C for 48 h.

Table 3. Scope of the Reaction with Respect to the Sulfinic acid[a]



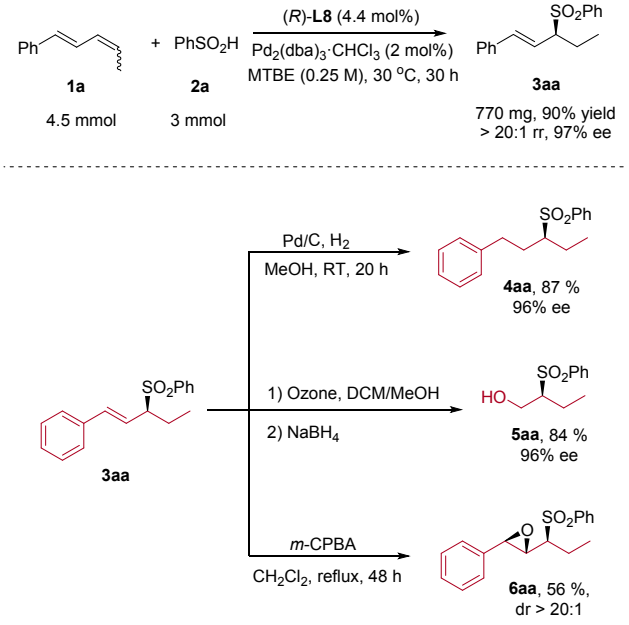
[a]See SI for details. Isolated yields are reported. The rr values were determined by ^{1}H NMR analysis of crude reaction mixtures. The ee values were determined by HPLC on a chiral stationary phase. [b]The concentration of **1a** was 0.4 M, and the reaction time was 72 h.

methyl) was prepared and subjected to the reaction conditions, sulfone **3na** was obtained with >20:1 regioselectivity and 96% enantioselectivity, although the yield was only 52%. Thus, the difference between steric bulk of R^1 and R^2 is another significant factor to control the regioselectivity. The R^2 group could be a longer alkyl group—ethyl (**3oa**), *n*-Pr (**3pa**), or *i*-Pr (**3qa**)—with little effect on the yield and selectivity. In addition, a substrate bearing an alkyl chain with a terminal OMe group afforded the desired product **3ra** in 80% yield with 17:1 rr and 96% ee. For a 1,3-diene with phenyl and CO_2Me as R^1 and R^2 group respectively, the hydrosulfonylation specifically occurred at the olefin adjacent to the ester group, furnishing **3sa** in 92% yield with excellent stereoselectivity. When R^2 was a H atom (**3ta**), the enantioselectivity dropped dramatically (to 75% ee), but the regioselectivity was unaffected. For this substrate, a 91% ee could be obtained by using **L6** as the ligand, but the yield and rr value were low. Cyclic allylic sulfone (**3ua**) and quaternary allylic sulfone (**3va**) could be prepared by

this method in good yield; however, the enantioselectivity was poor. Diary 1,3-diene in which one phenyl ring containing a *para*-MeO group and the other phenyl ring containing a *para*-CF_3 group was investigated for this reaction. We observed that both the regio- and enantioselectivity was moderate for this substrate (**3wa**/**3xa** = 2.8:1). Notably, the hydrosulfonylation preferred to occur at the olefin connecting to the electron-withdrawing phenyl ring, because a more stable Pd-π-allyl would be generated during the formation of this regioisomer.

Next we probed the scope of the reaction with respect to the sulfinic acid (Table 3). Phenyl sulfinic acids with a F or Cl atom or a Me, CF_3, or CN group on the phenyl ring were well-tolerated, giving sulfones **3ab**–**3aj**. For all of these substrates, the yields exceeded 75%, and the enantioselectivities were >95%. However, the reaction with 3,5-bis(trifluoromethyl)-benzenesulfinic acid showed a lower yield and a slightly lower ee (**3ai**). Hydrosulfonylation with aliphatic sulfinic acids gave lower yields than that with aromatic sulfinic acids. However, if the concentration of the 1,3-diene was increased to 0.4 M, cyclopropyl, isopropyl, benzyl, and even methyl sulfinic acids reacted smoothly with **1a**, generating the desired hydrosulfonylation products **3ak**–**3an** in good yields (42%–65%) with no decrease in regio- or enantioselectivity. The absolute configuration of the products was determined to be *S* by analogy with **3ab**, the structure of which was confirmed by means of X-ray crystallographic analysis.[13]

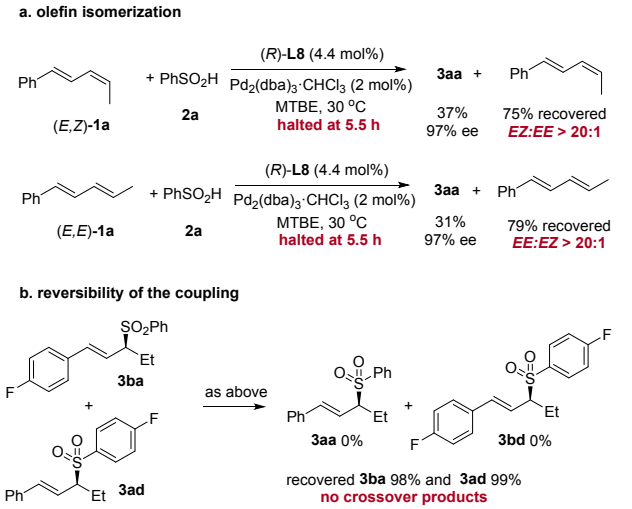
Scheme 2. Transformation of the Coupling Product[a]



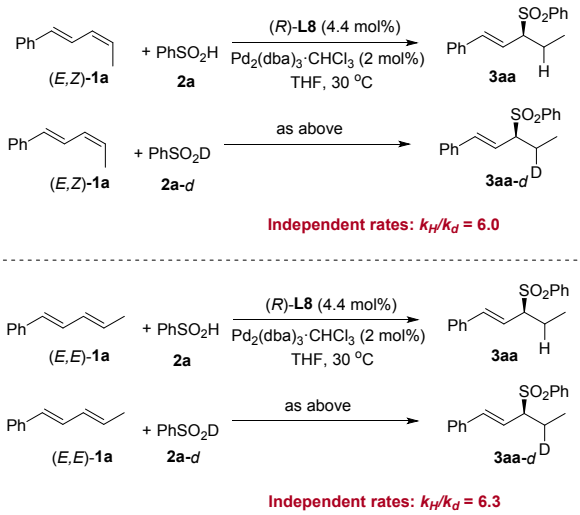
[a]See SI for details of the reaction conditions. *m*-CPBA = 3-chloroperoxybenzoic acid. Enantiomeric ratio of **6aa** was not determined.

2.3. Derivatization of the Product. The alkene group in the coupling product could be further manipulated to access various useful functionalities (Scheme 2). We first performed the hydrosulfonylation reaction in a 3 mmol scale, from which 770 mg **3aa** was obtained in a yield of 90%. Then using **3aa** as a substrate, some derivatization was demonstrated. Exposure of **3aa** under H_2 atmosphere with Pd/C catalyst, the hydrogenation product **4aa** was obtained in 87% yield. Cleavage the olefin with ozone followed by $NaBH_4$ reduction, affording β-hydroxyl chiral sulfone **5aa** in 84% yield. High enantioselectivities were maintained in the products during these transformations. In addition, epoxidation of **3aa** was achieved by treatment with *m*-CPBA in chloromethane under reflux, from which the resulting expoxide **6aa** was afforded in 56% yield with good diastereoselectivity.

Scheme 3. Control Experiments



Scheme 4. Determination of Kinetic Isotope Effect



2.4. Mechanistic Studies. To gain insight into the mechanism, control experiments were conducted. In this hydrosulfonylation reaction, a mixture of (*E,Z*)- and (*E,E*)-1,3-dienes was employed, but the enantioselectivity of the reaction was unaffected by the isomeric ratio of the starting material. One possible scenario is that the olefin undergoes rapid isomerization under the reaction conditions. To explore this possibility, we carried out experiments with isomerically pure starting material (Scheme 3a). Specifically, pure (*E,Z*)- and (*E,E*)-1,3-diene **1a** were prepared and separately subjected to the standard reaction conditions for 5.5 h, at which point the (*E,Z*)-**1a**/(*E,E*)-**1a** was determined. Interestingly, we did not observe any olefin isomerization during these reactions. These results indicated that the enantioconvergency is not a result of olefin isomerization.

Because allylic sulfones are prone to undergo oxidative addition of the C–S bond to the Pd(0) complex,[14] we examined the reversibility of the hydrosulfonylation reaction by subjecting a mixture of **3ba** and **3ad** to the standard conditions. However, no crossover products **3aa** and **3bd** were observed (Scheme 3b). These experiments suggest that this Pd-catalyzed hydrosulfonylation reaction is not a reversible transformation.

To gain more insight into the mechanism, we next performed a hydrosulfonylation with deuterium-labeled sulfinic acid **2a**-*d*, which afforded **3aa**-*d* with deuterium only at C1 (Scheme 3c). The deuterium ratio of H_α/H_β was close to the (*E,Z*)/(*E,E*) ratio of substrate **1a**. We then examined the deuterium experiment for pure (*E,E*)-**1a** and found only H_α at C1 was deuterium enriched. This result indicated that this hydrosulfonylation reaction is stereospecific *cis*-addition to the alkene and the H atom transfer step is irreversible. Furthermore, in previous studies of Pd-catalyzed hydrofunctionalization of 1,3-dienes, both C1 and C4 were found to be deuterium-enriched.[10e,f,h,] The difference between our results and these previously reported results suggests that our hydrosulfonylation reaction might proceeded via a distinct mechanism.

We also determined kinetic isotope effect (*KIE*, Scheme 4) for this reaction. Comparison of the initial rates of the catalytic hydrosulfonylation reactions of (*E,Z*)-**1a** with **2a** and **2a**-*d* in separate vessels revealed a *KIE* of 6.0; and a similar *KIE* value (6.3) was obtained for reactions of (*E,E*)-**1a**. These large *KIE* values suggest that cleavage of the O–H bond of the sulfinic acid was likely involved in the turnover-limiting step.

2.5. Computational Studies. In parallel with experiments, we also conducted density functional theory calculations to understand the mechanism. Previous studies of Pd-catalyzed hydrofunctionalization of 1,3-dienes indicated that a Pd-hydride migratory insertion of the olefin was involved.[10e–o] Because Pd-hydride is usually formed via protonation of Pd(0) by a Brønsted acid,[15] we began by calculating the energy profiles for this mechanism (Figure 2). In one possible pathway, the sulfur atom of the sulfinic acid coordinates to Pd(0), and the Pd-hydride is formed via a four-membered transition state **TS-2a**; the energy barrier for this step is 38.6 kcal/mol. A second possible pathway involves transition state **TS-2b** with a relatively low energy (25.0 kcal/mol), which has a five-membered ring with an oxygen atom coordinating to the Pd(0). The latter pathway is more energetically favorable.

Next we calculated the energy for the subsequent migratory insertion. Replacement the $PhSO_2^-$ with one molecule **1a** in **Int-3b** afford cationic intermediate **Int-4a**, which undergoes Pd-hydride migratory insertion via four-membered ring transition state (**TS-5a**)**.** This step has an activation barrier of 52.5 kcal/mol. We rationalized that the high energy of **Int-4a** and **TS-5a** might be attributed to the dissociation $PhSO_2^-$ from a neutral Pd complex. Thus we next calculated the migratory insertion pathway with $PhSO_2^-$ connecting to the Pd. Neutral complex $PhSO_2$-Pd-hydride **Int-4b** with a monoligated (*R*)-DTBM-Segphos was located and this intermediate has an energy of 38.5 kcal/mol.[16] The thereafter migratory insertion (via **TS-5b**) step indeed has a lower activation barrier than that of **TS-5a**. However, this possibility is also prohibited by the high activation barrier (40.2 kcal/mol). These calculations thus indicated that the Pd-hydride migratory insertion pathway is energetically unfavorable.

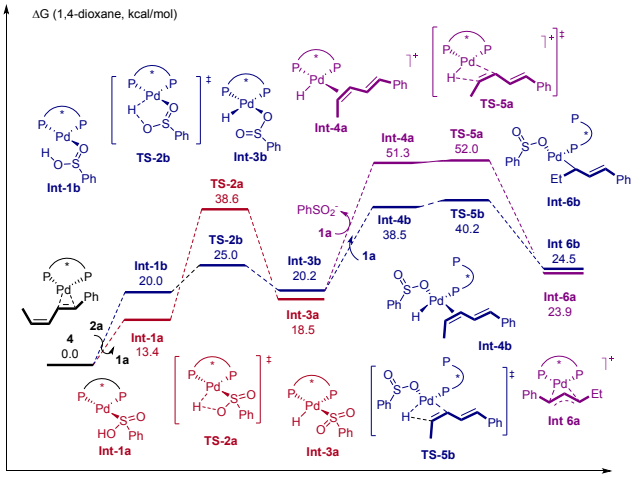


Figure 2. Energy profiles for pathways involving Pd-hydride migratory insertion.

Haven excluded the Pd-hydride involved pathway, we conjectured that the hydrogen atom might be transferred directly from the sulfinic acid to the 1,3-diene via a LLHT process.[12] To test this hypothesis, we carried out calculations for square planar complex **Int-7a**, in which Pd is coordinated with one of the P atoms of (*R*)-**L8**, the S atom of sulfinic acid, and one double bond of the 1,3-diene substrate. Starting from **Int-7a**, which has an energy of 11.6 kcal/mol, we calculated the energy profile for the pathway that leads to (*S*)-**3aa**, the major enantiomer generated from (*E,Z*)-**1aa** (indicated in blue in Figure 3). In this pathway, **Int-7a** is first converted to **Int-9a** by LLHT from the sulfinic acid to the 1,3-diene. The transition state for this step, **TS-8a**, features a six-membered palladacycle and has an energy of 20.9 kcal/mol. **Int-9a** is then transformed to more thermally stable intermediate **Int-11a** via two ligand rearrangements (S to O and π-allyl η^3 to η^1). Finally, **Int-11a** undergoes C–S reductive elimination[17] via

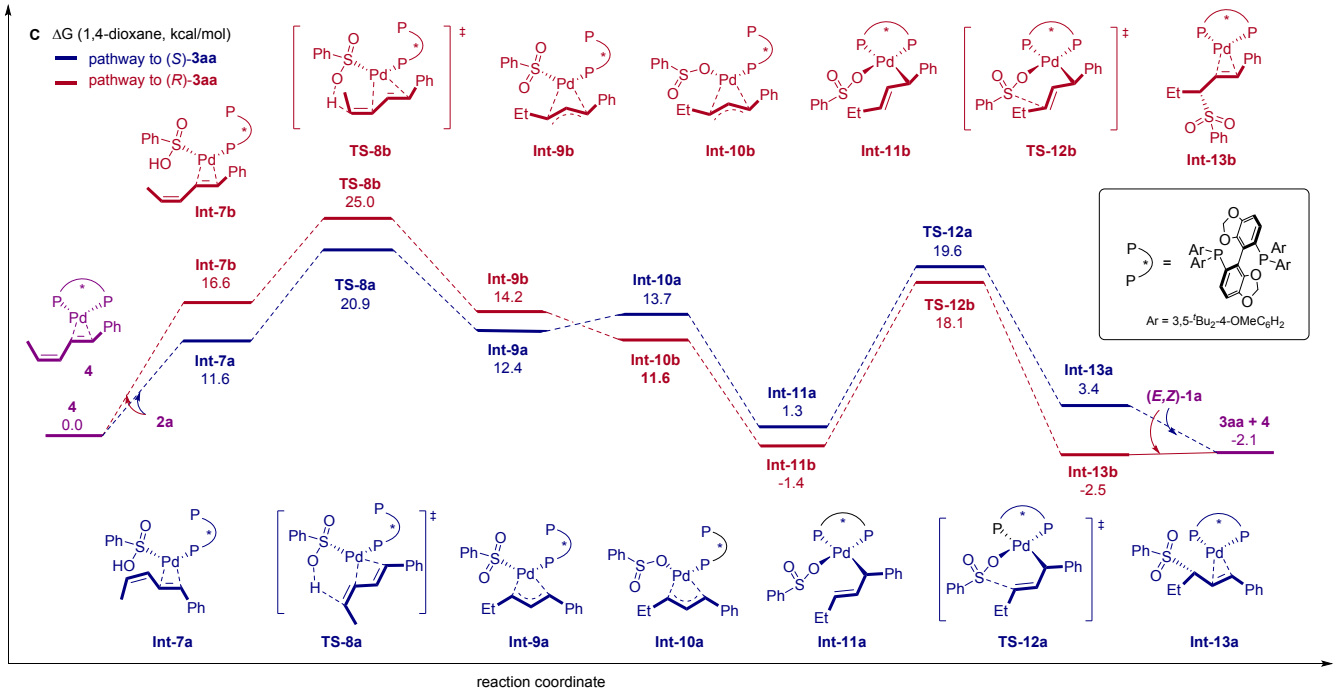


Figure 3. Energy profile for hydrosulfonylation of (*E,Z*)-1,3-diene **1a** with sulfonic acid **2a**. Calculations were carried out at the M06/6-311++g(d,p)/SDD//B3LYP-D3/6-31g(d)/Lanl2dz level of theory.

six-membered-ring transition state **TS-12a** to deliver the hydrosulfonylation product, a process with an energy barrier of 19.6 kcal/mol. The LLHT step has a higher energy barrier than the subsequent C–S reductive elimination step. Thus, the LLHT step is irreversible, which is consistent with the experimental observation that no isomerization of the (*E,Z*)-olefin to the (*E,E*)-olefin occurred during the reaction. We computed the energy profile of the pathway that leads to the minor enantiomer (*R*)-**3aa** (indicated in red in Figure 3), which is similar to that for the pathway leading to (*S*)-**3aa**. Notably, the energy of transition state **TS-8b** is 25.0 kcal/mol, which is 4.1 kcal/mol higher than the energy of **TS-8a**. This is in good agreement with the excellent enantioselectivities observed in the experiments. Therefore, the irreversible LLHT step is both turnover-limiting and enantioselectivity-determining. This result is consistent with the large *KIE* observed (Scheme 4).

2.5. Origin of the Enantioselectivity. In this hydrosulfonylation reaction, high enantioselectivity was observed regardless of the (*E,Z*)-/(*E,E*) ratio of the starting **1a**. As mentioned above, we ruled out the possibility of olefin isomerization during the reaction. Therefore, we speculated that the reaction occur stereoconvergently; that is, both (*E,Z*)-**1a** and (*E,E*)-**1a** reacted to afford the same enantiomer of the product, (*S*)-**3aa**. To explore the origin of the enantioselectivity, we also calculated the energies of the transition states of LLHT step for reaction

of (*E,E*)-**1a** to afford (*S*)- and (*R*)-**3aa** (Figure 4, see SI for full energy profile). Comparison of the energies of transition states **TS-8c** and **TS-8d** indicated that the formation of (*S*)-**3aa** was favored over the formation of (*R*)-**3aa** by 3.6 kcal/mol. Thus, both (*E,Z*)- and (*E,E*)-**1a** underwent the enantiodetermining LLHT step from the same prochiral face of the olefin, giving (*S*)-**3aa** as the predominant product.

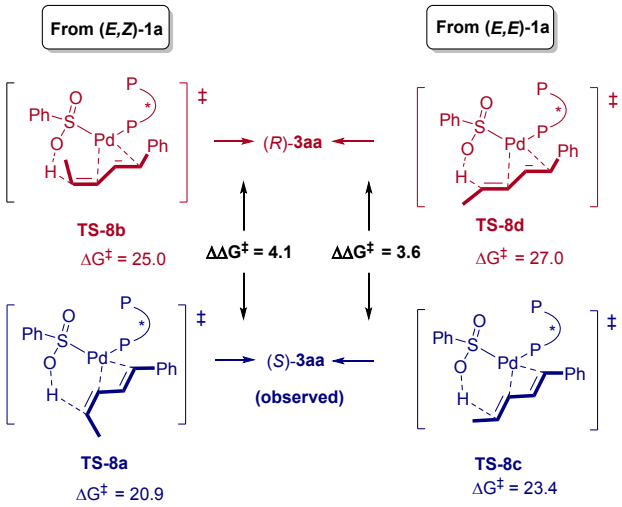


Figure 4. Calculated energies of transition states of LLHT step for reactions of (*E,E*)- and (*E,Z*) **1a**.

The calculated structures of **TS-8a**, **TS-8b**, **TS-8c** and **TS-8d** are shown in Figure 5. Comparing the structures of **TS-8a** and **TS-8b**, at least three factors contributed to the difference in energy between them. First, in **TS-8b**, there is substantial repulsion between the olefinic C–H of the substrate and the *t*-Bu group of the ligand, whereas no such repulsion is observed in **TS-8a** (interatom distances of 2.16, 2.18, and 2.21 Å versus 2.92, 3.07, and 3.34 Å). Second, steric repulsion between H_c of the substrate and one H atom in the phenyl ring of this ligand is stronger in **TS-8b** than in **TS-8a** (2.11 Å versus 2.44 Å). Third, 1,3-allylic strain is largely released in **TS-8a** because the distance between the Me group and the olefinic C–H_b is 2.33 Å, whereas this distance is 2.12 Å in substrate (*E,Z*)-**1a**. Less 1,3-allylic strain is released upon formation of **TS-8b**, in which the distance between the Me group and the olefinic C–H_b is 2.27 Å. This result is consistent with the observed low ee value of **3pa** (75%, Table 2), the formation of which does not involve the relief of such allylic strain.

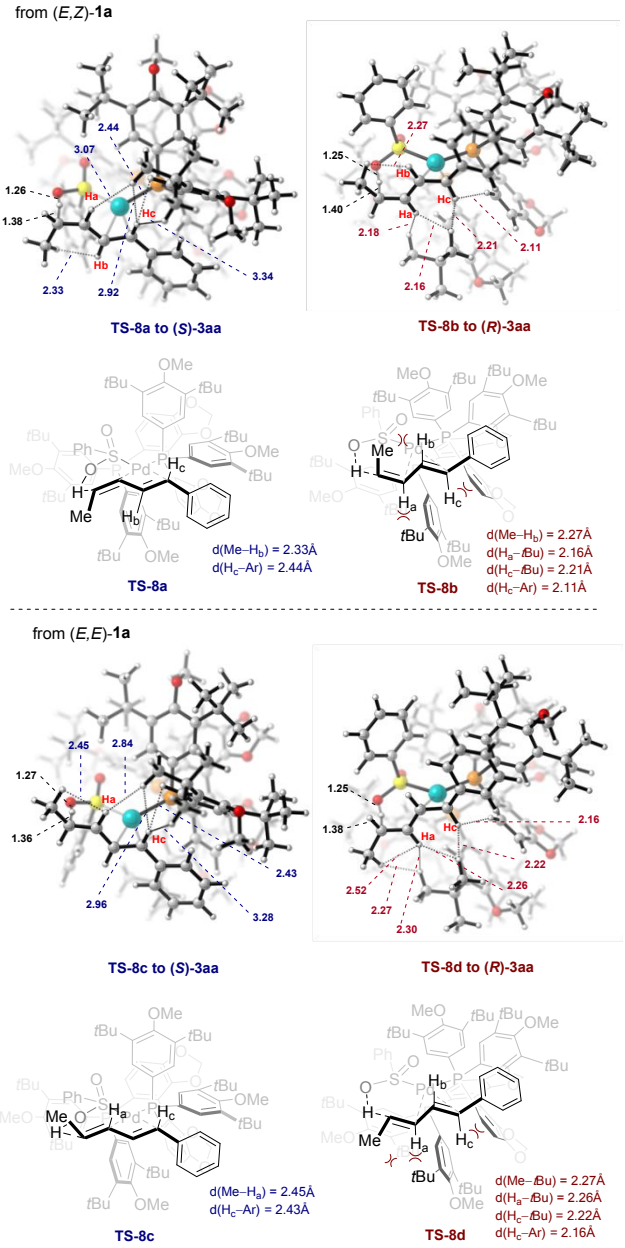


Figure 5. Structures of transition states for LLHT.

Comparison of the structures of **TS-8c** and **TS-8d** (Figure 5) reveals that the aforementioned steric repulsion between the substrate and ligands is also present in **TS-8d**; however , it is much weaker in **TS-8c** (interatomic distances of 2.16, 2.22, 2.26, and 2.30 Å versus 2.43, 2.84, 2.96, and 3.28 Å). The 1,3-allylic strain relief that occurs upon formation of **TS-8d** is considerable; the distance between the Me group and the olefinic C–H_a in this transition state is 2.52 Å, which is slightly longer than the distance in substrate (*E,E*)-**1a** (2.44 Å). The relief of 1,3-allylic strain associated with the formation of **TS-8c** is negligible (2.45 Å). Nevertheless, in **TS-8d**, we noticed a strong repulsive interaction between the Me and *t*-Bu groups (the shortest distance between these two groups is 2.27 Å), whereas no such repulsion was observed in **TS-8c**. This repulsion likely contributes strongly to the higher energy of **TS-8d**.

These analysis suggests that the *t*-Bu groups of the ligand played a key role in controlling the enantioselectivity. To verify this finding from computation, we tested the catalytic hydrosulfonylation reaction with (*R*)-DM-Segphos, in which the *t*-Bu groups of (*R*)-DTBM-Segphos was replaced by Me groups. Indeed, this reaction afforded **3aa** with significantly lower enantioselectivity (80% ee versus 97% ee; Figure 6). Notably, the yield of **3aa** obtained with (*R*)-DM-Segphos (28%) was markedly lower than that with (*R*)-DTBM-Segphos. Finally, when we used (*R*)-Segphos, in which both of the *t*-Bu groups of (*R*)-DTBM-Segphos were replaced by H atoms, the yield of **3aa** was <5%. This result was probably due to the fact that the less sterically hindered ligand coordinated to the Pd atom in a bidentate fashion, thus prohibiting the LLHT step.

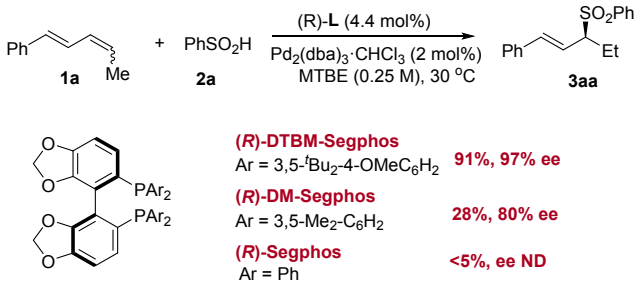


Figure 6. Relationship between enantioselectivity and ligand steric bulk.

3. CONCLUSION

In summary, we have developed a protocol for (*R*)-DTBM-Segphos/Pd-catalyzed enantioselective hydrosulfonylation reaction of 1,3-dienes with sulfinic acids. This regio- and enantioselective transformation provides otherwise-challenging-to-obtain 1,3-unsymmetrical chiral allylic sulfones in a step- and atom-economical fashion. Mechanistic studies indicated that the reaction does not involves a Pd-hydride. Computational studies suggested that the reaction is instead initiated by a LLHT, which is followed by C–S bond reductive elimination via a six-membered-ring transition state. Steric repulsion between the olefinic C–H of the substrate and the *t*-Bu group of the (*R*)-DTBM-Segphos ligand was found to be a key enantiodetermining factor. Improvement of the catalyst activity and further mechanistic studies are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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