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COMMUNICATION

Palladium-Catalyzed Asymmetric Hydrosulfonylation of 1,3-Dienes with Sulfonyl Hydrazides

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Abstract: A highly enantio- and regioselective hydrosulfonylation of 1,3-dienes with sulfonyl hydrazides has been realized by using palladium catalyst containing monodentate chiral spiro phosphoramidite ligand. The reaction provided efficient approach to the synthetically useful chiral allylic sulfones. Mechanistic studies suggest that the reaction proceeds through a formation of allyl hydrazine intermediate and subsequent rearrangement to the chiral allylic sulfone product. The transformation of the allyl hydrazine intermediate to the product is enantioselectivity-determining step.

Optically active organic sulfur compounds occur in various natural and bio-active systems.[1] In particular, the chiral allylic sulfones exhibit rich biological activities such as antibacterial, and antiviral activities (Figure 1).[2] Many efforts have been devoted to the development of the methodology for the synthesis of chiral allylic sulfones. The asymmetric allylic substitution with sulfur reagents[3] and asymmetric hydrogenation reaction[4] are demonstrated to be efficient methods for the synthesis of chiral allylic sulfones. Transition metal-catalyzed asymmetric hydrofunctionalization reactions of 1,3-dienes, allenes, and alkynes with different nucleophiles or electrophiles provided a straightforward and atom-economical approach to the chiral allylic compounds.[5] Among them, the hydrothiolation has been applied in the enantioselective synthesis of chiral allylic sulfones, however one oxidation step was required. For example, in 2014, Breit and co-workers developed a Rh-catalyzed enantioselective hydrothiolation of allenes, followed by oxidation of the products, giving chiral allylic sulfones (Scheme 1a).[6] In 2018, Dong et al. reported an enantioselective hydrothiolation of 1,3-dienes, affording 1,2-Markovnikov sulfide products, which could be converted to chiral allylic sulfones by oxidation (Scheme 1b).[7] However, in contrast, the synthesis of chiral allylic sulfone compounds from direct enantioselective hydrosulfonylation of dienes remains a challenge. As a part of our continuous research interests in developing methods for the synthesis of chiral allylic compounds through asymmetric hydrofunctionalization of dienes,[8] we studied Pd-catalyzed enantioselective hydrosulfonylation of 1,3-dienes with sulfonyl hydrazides and obtained chiral allylic sulfones with perfect 3,4-Markovnikov regioselectivity and high enantioselectivity (Scheme 1c).

We first studied the reaction of *p*-toluenesulfonyl hydrazide (**2a**) (1.0 equiv) with 1-phenylbutadiene (**1a**) (2.0 equiv) using nickel catalysts we developed in the hydroarylation of styrenes and 1,3-dienes.[9] However, although various chiral mono- or bisphosphine ligands have been evaluated, the hydrosulfonylation product **3a** was obtained in only moderate yield and up to 56% ee (for details, see Supporting Information).It is delighted that when we use palladium catalyst bearing monodentate chiral spiro phosphoramidite ligand **L4** the hydrosulfonylation product, 3,4-Markovnikov branched allylic sulfone **3a**, was obtained in 85%yield and 64% ee (Table 1, entry 4). Other monodentate chiral spiro phosphorus ligands or

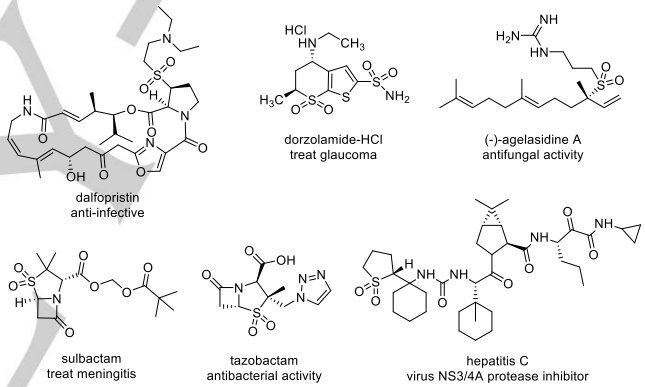
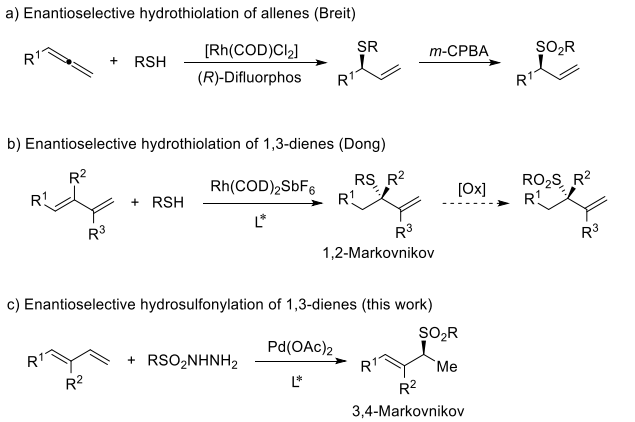


Figure 1. Examples of natural products and drugs containing chiral sulfone motifs



Scheme 1. Enantioselective hydrofunctionalization of unsaturated hydrocarbons for the synthesis of chiral allylic sulfones

diphosphine ligand gave low enantioselectivity (entries 1–3 and 5). Solvent's evaluation showed that the diglyme is the choice of solvent, giving higher enantioselectivity (75% ee, entry 8). The enantioselectivity of reaction was increased to 89% ee by adding

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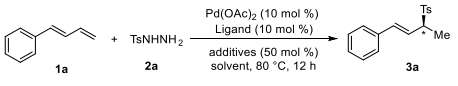
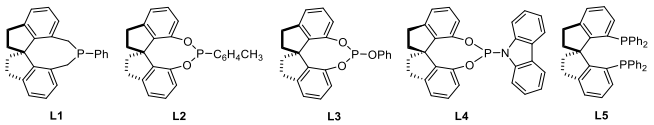
p-toluenesulfonic acid (50 mol %) (entry 11),[10] and was further enhanced to 93% ee at a lower temperature (60 °C) (entries 13 and 14).

Table 1. Enantioselective hydrosulfonation of diene, Optimization of reaction conditions[a]



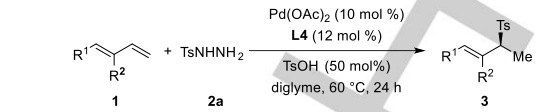


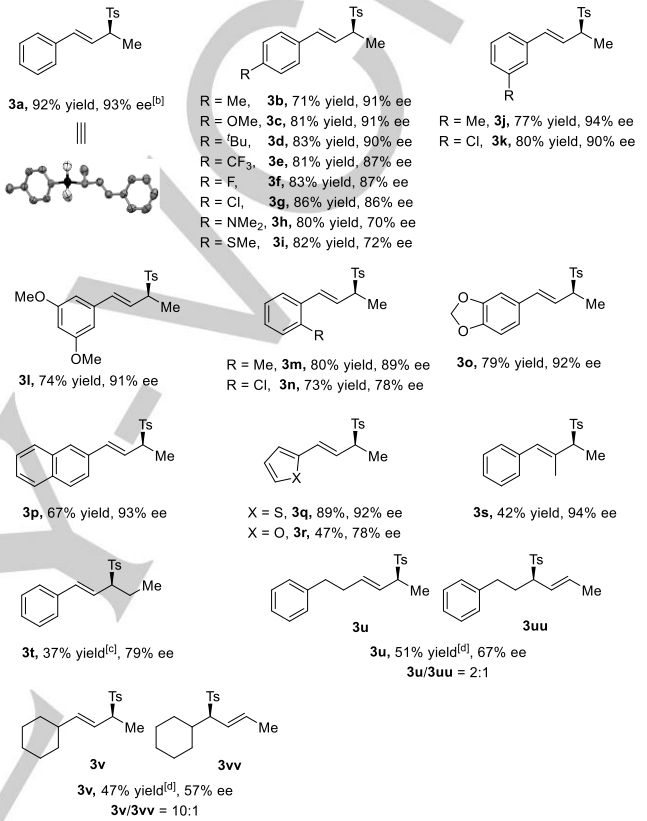
Entry	Ligand	additives	Solv.	yield (%)[b]	ee (%)[c]
1	**L1**	none	1,4-dioxane	95	2
2	**L2**	none	1,4-dioxane	41	2
3	**L3**	none	1,4-dioxane	93	37
4	**L4**	none	1,4-dioxane	85	64
5	**L5**	none	1,4-dioxane	64	5
6	**L4**	none	toluene	81	44
7	**L4**	none	THF	85	74
8	**L4**	none	diglyme	84	75
9	**L4**	PhCOOH	diglyme	85	63
10	**L4**	$PhCH_2COOH$	diglyme	89	70
11	**L4**	TsOH	diglyme	91	89
12	**L4**	$(PhO)_2P(O)OH$	diglyme	90	65
13[d]	**L4**	TsOH	diglyme	73	93
14[d],[e]	**L4**	TsOH	diglyme	92	93

[a] Reaction conditions: 1-phenylbutadiene (**1a**) (0.2 mmol), *p*-toluenesulfonyl hydrazide (**2a**) (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand (0.01 mmol), additive (0.05 mmol), solvent (0.5 mL) at 80 °C for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] At 60 °C, 24h. [e] Use 0.012 mmol ligand.

Having the optimized reaction conditions, we evaluated the substrate scope of the reaction. Various 1,3-dienes can react with *p*-toluenesulfonyl hydrazide (**2a**) to produce allylic sulfones (Table 2). The aromatic dienes showed perfect regioselectivity in the reaction and only formed 3,4-Markovnikov addition product. It is noteworthy that the *E*/*Z* mixture of 1,3-diene **1a** gives the same result as the pure *E*-isomer. The absolute configuration of the product **3a** was determined by X-ray diffraction analysis of single crystal. Most of the tested *para*- and *meta*-substituted aromatic dienes (**1b**–**1g** and **1j**–**1l**) reacted with hydrazide **2a** to afford hydrosulfonylation products in good yield (71–86%) and high enantioselectivity (86–94% ee), however the substrates containing *para*-dimethylamino (**1h**) and *para*-methylthio (**1i**) groups have slightly lower enantioselctivity (70% ee and 72% ee, respectively). The *ortho*-substituted aromatic dienes **1m** and **1n** have 89% ee and 78% ee of enantioselectivity. The dienes with 3,4-methylenedioxyphenyl (**1o**), 2-naphthyl (**1p**), thienyl (**1q**) and furyl (**1r**) also showed good yield and high enantioselectivity. 1,2-Disubstituted diene **1s** also worked in high enantioselectivity (94% ee), albeit with moderate yield. The internal diene **1t** afforded 79% ee of enantioselectivity, but with a poor yield (37%) in the present reaction conditions. Besides aromatic dienes, the aliphatic 1,3-dienes (**1u** and **1v**) were investigated in the hydrosulfonylation reaction with hydrazide **2a**, however, a mixture of 3,4- and 1,2-addition products was obtained.

Table 2 Enantioselective hydrosulfonylation with various dienes[a]





[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand **L4** (0.012 mmol), *p*-toluenesulfonic acid (0.05 mmol), diglyme (0.5 mL) at 60 °C for 24 h. Isolated yield. Regioselectivity of product was determined by 1H NMR. [b] *E*/*Z* configuration of aromatic dienes had no effect on the yield and selectivity of the reaction. [c] Temperature: 80 °C. [d] Combined yield.

We then studied the scope of sulfonyl hydrazides **2**. As shown in Table 3, variation of electronic effect of the phenyl sulfonyl hydrazides had no influence on both yield and enantioselectivity of hydrosulfonylation reaction (**2a**–**2f**). 1-Naphthyl sulfonyl hydrazide (**2g**) showed moderate yield and good enantioselectivity. In addition to aromatic sulfonyl hydrazides, aliphatic sulfonyl hydrazides (**2h**–**2l**) can also be efficient sulfonylation reagents, albeit the 3-chloropropyl sulfonyl hydrazide (**2l**) gives a lower yield (51%).

To probe the reaction mechanism, we conducted several control experiments (see Supporting Information). The reaction was stopped at 1 hour and the racemic hydrazide intermediate **3′** was isolated as main product (see SI 6a). When the intermediate **3′** was treated under standard reaction conditions, sulfone product **3a** was obtained in 98% yield with 91% ee (see SI 6b). These two experiments indicated that the enantioselectivity of the reaction was determined during the conversion of hydrazide intermediate **3′** to sulfone product **3a**,[11] ruling out the process of chirality transfer of the intermediate **3′**.[12] A cross reaction of 4-

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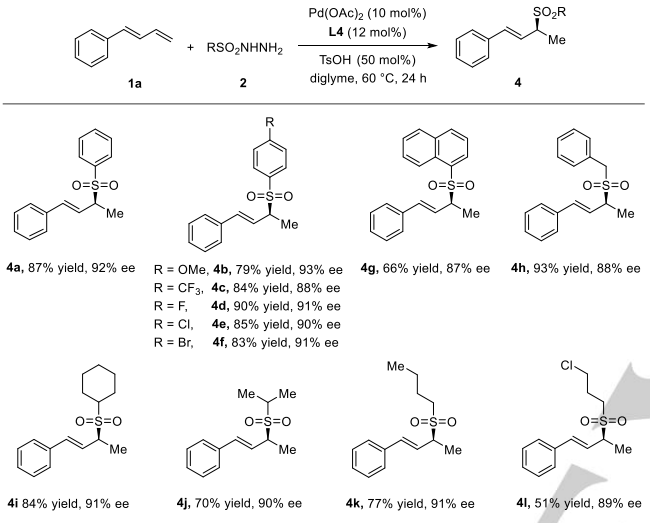
methoxylphenyl buta-1,3-diene (**1c**) and the intermediate **3′** afforded a mixture of sulfones **3a** (47%, 88% ee) and **3c** (46%, 91% ee), indicating that the transformation of diene to the intermediate **3′** is reversible (see SI 6c). Tracing the reaction process showed that the intermediate **3′** was quickly accumulated at about half an hour, and then was gradually transformed into the product **3a** (see SI 6d). It is worth noting that when the reaction was performed without adding *p*-toluenesulfonic acid, the intermediate **3′** was obtained with 67% yield and 78% ee after 5 hours (see SI 6e). This means that the addition of the acid changes the reaction pathway, and accelerates the conversion of the intermediate **3′** to product **3a**.

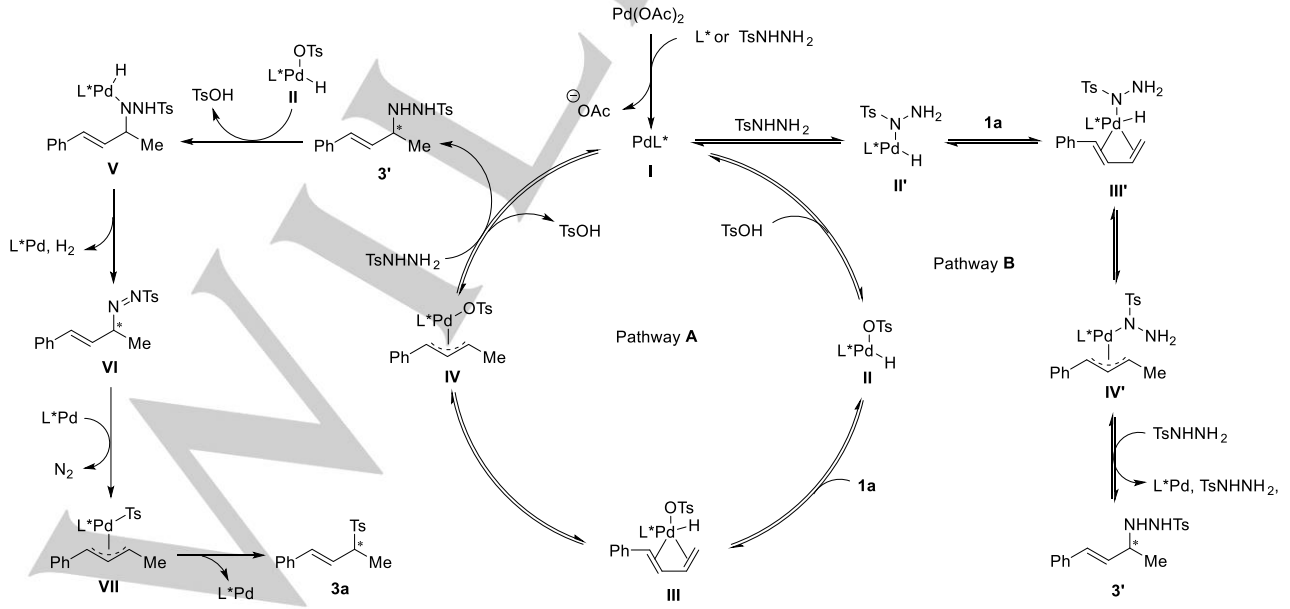
Table 3 Enantioselective hydrosulfonylation with various sulfonyl hydrazides[a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand L4 (0.012 mmol), *p*-toluenesulfonic acid (0.05 mmol), diglyme (0.5 mL) at 60 °C for 24 h. Isolated yield.

Based on aforementioned experiments and previous reports on the Pd-catalyzed hydrofunctionalization of conjugated dienes,[13] we proposed a mechanism for the enantio- and regioselective hydrosulfonylation of 1,3-dienes with sulfonyl hydrazides (Scheme 2). The reduction of Pd(II) complex by hydrazide formed Pd(0) species **I**. Depending on adding TsOH or not, there are two possible paths that generate intermediate **3′**: Path **A**, with TsOH. The Pd(0) underwent oxidative addition with TsOH to yield Pd−H species **II**, which coordinated with diene **1a** followed by insertion of hidride into terminal double bond, providing Pd-π-allyl complex **IV**. The nucleophilic attack of sulfonyl hydrazide to the complex **IV** gave intermediate **3′** with low enantioselectivity (see SI 6a); Path **B**, without TsOH. The Pd(0) underwent oxidative addition with sulfonyl hydrazide to yield Pd−H species **II′**, which coordinated with diene **1a** to form intermediate **III′**. The insertion of Pd−H of **III′** into the terminal double bond of diene generated Pd-π-allyl complex **IV′**, which was attacked by sulfonyl hydrazide to form **3′** with 78% ee (see SI 6e). Since $TsNHNH_2$ is more than TsOH in the beginning of reaction, the pathway B was dominant. As the reaction progresses, the $TsNHNH_2$ was consumed and the pathway A gradually became dominant, and the ee value of intermediate **3′** dropped (see SI 6d). The ligand exchange of Pd(II) species **II** with intermediate **3′**, followed by β-H elimination generated diazene intermediate **VI**.[11] The oxidative addition of Pd(0) with **VI** and releasing nitrogen produced the intermediate **VII**. Finally, the reductive elimination of **VII** delivered the hydrosulfonylation product **3a** and regenerated Pd(0) species **I**.[14]

In summary, we developed a highly enantio- and regioselective hydrosulfonylation of 1,3-dienes with sulfonyl hydrazides catalyzed by palladium complex of monodentate chiral spiro phosphoramidites. The reaction provides a new strategy for the synthesis of chiral allylic sulfones in high enantioselectivity. Mechanistic studies suggest that the reaction proceeds through a formation of allyl hydrazine intermediate and subsequent conversion of intermediate to chiral allylic sulfone product. The enantioselectivity of the reaction was controlled at the reductive elimination step.



Scheme 2. Proposed mechanism

Acknowledgements

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Keywords: asymmetric hydrosulfonylation • 1,3-dienes • sulfonyl hydrazides • palladium • chiral sulfone

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[14] During the preparation of this manuscript, an enantioselective hydrosulfonylation of internal 1,3-dienes with sulfinic acids using Pd/DTBM-Segphos catalyst was reported by Zi et al.: 10.1021/jacs.0c05976. In that research, the internal dienes performed well, and is complementary to this work.

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