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Palladium-Catalyzed Enantioselective Alkenylation of Sulfenate Anions

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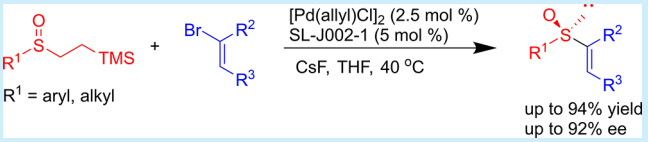
Supporting Information

ABSTRACT: A novel approach to synthesize enantioenriched alkenyl/aryl sulfoxides is achieved by using CsF to generate sulfenate anions and conducting the catalytic enantioselective alkenylation with [Pd(allyl)Cl]$_2$/(2*R*)-1-[(1*R*)-1-[bis(1,1-dimethylethyl)phosphino]ethyl]-2-(diphenylphosphino)ferrocene (SL-J002-1). A wide variety of sulfoxides bearing sensitive functional groups are produced with high yields (up to 94%) and enantioselectivities (up to 92%).



Enantioenriched sulfoxides are key structural motifs in medicinal chemistry that are present in a broad range of natural products,[1] bioactive compounds,[2] and marketed drugs.[3] Recently, they have also attracted attention as ligands and been successfully applied in asymmetric catalysis.[4] Vinyl sulfoxides are particularly useful, because they can be electrophilic or nucleophilic at the α-position[5] and are electrophilic at the β-position.[6] The synthetic utility of sulfoxides is demonstrated by their use as oxosulfonium ylides[7] and in Pummerer-type reactions.[8]

Traditionally, enantioenriched sulfoxides are synthesized in two ways: nucleophilic substitution with chiral sulfinyl amides or esters, and catalytic enantioselective oxidation of sulfides. The well-known Andersen procedure[9] utilizes optically pure menthyl *p*-tolylsulfinates, which require several recrystallizations to achieve enantiopurity. Organometallic reagents, including organolithium and Grignard reagents, are required in this procedure. These reagents may racemize the sulfoxide stereocenter and limit the substrate scope.[10] The most popular enantioselective sulfide oxidation protocol was pioneered by Kagan and Modena.[11] This approach gives poor results when the substituents on the sulfur are similar in size. Chemoselectivity can also be poor if over-oxidation to the sulfone occurs.[11c]

A novel method to synthesize enantioenriched sulfoxides was developed by Dong and Houk.[12] They utilized dynamic kinetic resolution (DKR) of allylic sulfoxides relying on a Mislow–Evans rearrangement coupled with a catalytic asymmetric hydrogenation (Scheme 1a). Subsequently, a hydrogenative kinetic resolution of vinyl sulfoxides using a Rh/phosphine-phosphite complex as a catalyst was demonstrated by Vidal-Ferran[13] (Scheme 1b). Both methods give high enantioselectivities to afford specific types of chiral sulfoxides (*n*-propyl sulfoxides or ethyl sulfoxides).

Another approach to enantio-enriched sulfoxides utilized the generation of sulfenate anions (R–SO$^-$)[14] in transition-metal-catalyzed cross-coupling reactions.[15] The first examples were reported by Poli and Madec in 2007 (Scheme 1c).[15a] The potential utility of this work was diminished by the limited substrate scope and modest enantioselectivities (40%–80%). We recently[16] developed a method to generate sulfenate anions from benzyl sulfoxides with yields as high as 95% and enantioselectivities up to 94% (Scheme 1d). This system was limited to the preparation of enantio-enriched diaryl sulfoxides that were stable to the basic conditions (NaO^{t}Bu). An accompanying computational study highlighted the importance of isomerization between *O*- and *S*-bound palladium sulfenate anions in the enantio-determining step. Very recently, Zhang[17] designed a new chiral ligand for the arylation of a variety of sulfenate anions in high yields (45%–96%) and very high enantioselectivities (86%–99%), again using only aryl electrophiles (Scheme 1e). Herein, we report a very mild palladium-catalyzed coupling of sulfenate anions with both alkenyl and aryl bromides to afford enantioenriched sulfoxides (Scheme 1f), expanding the scope of chiral sulfoxides accessible using enantioselective coupling reactions.

We recently reported the formation of racemic diaryl and aryl alkyl sulfoxides in excellent yields from 2-(trimethylsilyl)-ethyl substituted sulfoxides via a palladium-catalyzed cross-coupling reaction[15g,h] (Scheme 2). The advantage of this process is that CsF is a milder base than NaO^{t}Bu. Therefore, we envisioned that these mild conditions would be more suitable to an efficient asymmetric protocol and enable us to expand the substrate scope of sulfenate anions in enantioselective reactions with vinyl halides.

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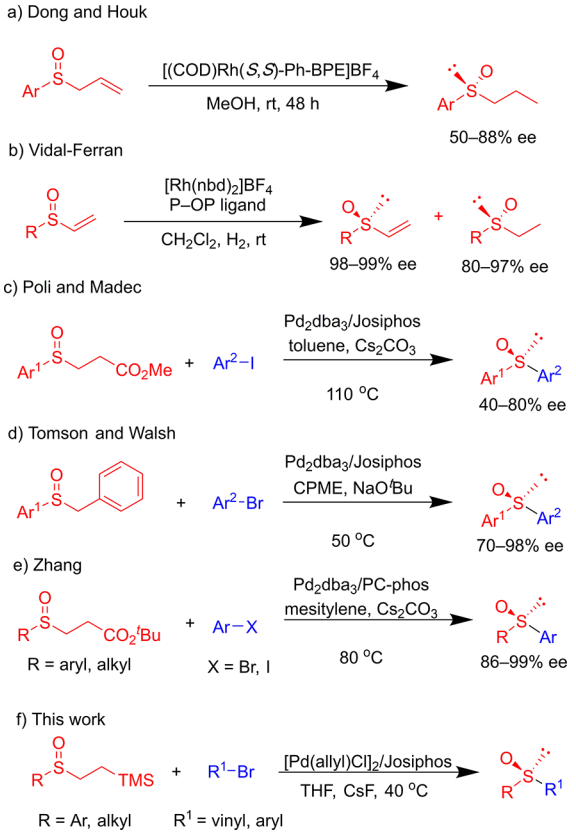
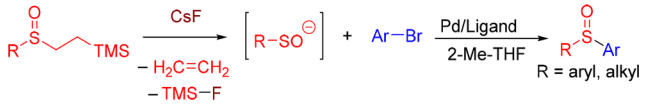
Scheme 1. Methods To Synthesize Chiral Sulfoxides



Scheme 2. Substituted 2-(Trimethylsilyl)ethyl Sulfoxide as the Sulfenate Anion Precursors for Pd-Catalyzed Cross-Couplings with Aryl Bromides

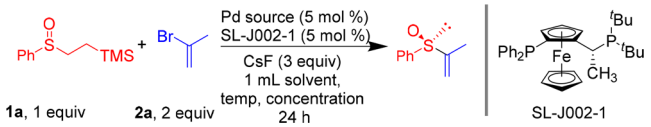


We initially screened the reaction between 2-(trimethylsilyl)ethyl phenyl sulfoxide (**1a**, 1 equiv) and 2-bromopropene (**2a**, 2 equiv) with 5 mol % $Pd(dba)_2$, 24 chiral phosphine ligands (10 mol % for monodentate ligands and 5 mol % for bidentate ligands) and CsF (3 equiv) in 100 μL 2-Me-THF at 80 °C for 24 h (see the Supporting Information for details). Of all the ligands screened, SL-J002-1 was the most promising. in terms of yield and enantioselectivity (Table 1). It was then used on a larger scale using 0.1 mL of 0.5 M solvent, providing 79% assay yield (AY, determined by ^{1}H NMR integration with CH_2Br_2 as the internal standard) and moderate enantioselectivity (71%, Table 1, entry 1, ee determined by chiral phase SFC; see the Supporting Information). A survey of palladium sources and solvents showed that $[Pd(allyl)Cl]_2$ in THF gave slightly higher yields with up to 79% ee (Table 1, entries 2 and 3). When the reaction temperature was decreased to 50 and 40 °C, the yield was maintained (85%–87%) and ee increased to 84% and 89%, respectively (Table 1, entries 4 and 5). However, at 27 °C, the yield fell to 10% with 93% ee (Table 1, entry 6). We found that changing the concentration did not improve the yield or ee (Table 1, entries 7 and 8). Therefore, our optimized conditions for the palladium-catalyzed enantioselective vinylation of sulfenate anions employ 2.5 mol % $[Pd(allyl)Cl]_2$ with 5 mol % SL-J002-1 as the catalyst, **1a** (0.5 mmol), **2a** (1.0 mmol) and CsF (1.5 mmol) in 1 mL THF at 40 °C for 24 h (Table 1, entry 5).

With the optimized conditions in hand, a variety of sulfenate anions were generated from aryl 2-(trimethylsilyl)ethyl sulfoxides in the presence of vinyl bromide **2a** (Scheme 3). 2-(Trimethylsilyl)ethyl sulfoxides bearing electronegative or electron-withdrawing groups, such as 4-F, 4-Cl, 4-CF_3, and 4-NO_2, provided the corresponding products in 82% (**3b**), 78% (**3c**), 71% (**3d**), and 51% (**3e**) yields with 87%–91% ee. The electron-donating 4-methoxy sulfoxide **2f** furnished the product (**3f**) in 94% yield with 83% ee, using 10 mol % catalyst. Sterically hindered aryl 2-(trimethylsilyl)ethyl sulfoxides bearing 2-tolyl or 1-naphthyl provided products in 78%–80% yield, but with reduced enantioselectivities of 79% (**3g**) and 63% (**3h**). Sulfoxides with heteroaryl moieties are very important in medicinal chemistry but can be difficult to prepare by traditional methods, because of overoxidation.[16] The 4-pyridyl-substituted sulfenate anion that formed **3i** was a good substrate, giving 68% yield and 91% ee.

Next, the scope of alkenyl electrophiles was explored with **1a** under the optimized conditions (Scheme 4). We first examined styrenyl bromides but yields under the optimized conditions were low. After screening a series of additives, we found that the yields improved by adding 15-crown-5 or increasing the reaction temperature. Enantioenriched sulfoxides derived from styrenyl bromides bearing 4-F (**3j**) or electron-donating groups (**3k**, **3l**, **3m**) gave 70%–91% yield and 70%–83% ee. (*Z*)-2-

Table 1. Optimization of Asymmetric Vinylation of Sulfenate Anions



entry	Pd source	solvent	temperature, t [°C]	concentration [M]	assay yield, AY[a] [%]	enantiomeric excess, ee [%]
1	$Pd(dba)_2$	2-Me-THF	80	0.5	79	71
2	$Pd(dba)_2$	THF	80	0.5	83	77
3	$[Pd(allyl)Cl]_2$	THF	80	0.5	85	79
4	$[Pd(allyl)Cl]_2$	THF	50	0.5	85	84
5	$[Pd(allyl)Cl]_2$	THF	40	0.5	87 (85[b])	89
6	$[Pd(allyl)Cl]_2$	THF	27	0.5	10	93
7	$[Pd(allyl)Cl]_2$	THF	40	0.25	30	87
8	$[Pd(allyl)Cl]_2$	THF	40	1.0	80	88

[a]As determined by ^{1}H NMR, using 0.1 mmol CH_2Br_2 as internal standard. [b]Isolated yield.

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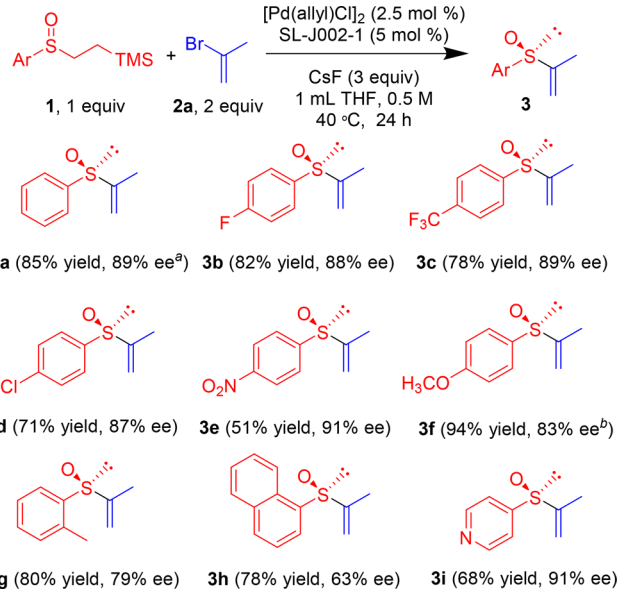
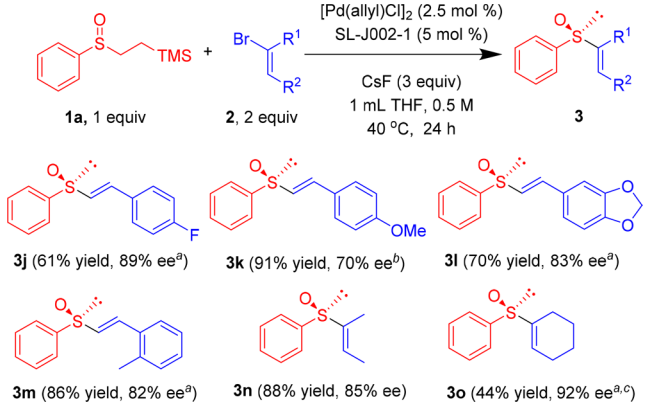
Scheme 3. Substrate Scope of Aryl 2-(trimethylsilyl)ethyl Sulfoxides in Pd-Catalyzed Enantioselective Cross-Couplings with 2a



[a]One mmol reaction was conducted and gave **3a** with 79% yield and 89% ee. [b][Pd(allyl)Cl]$_2$, 5 mol %; SL-J002-1, 10 mol %.

Scheme 4. Substrates Scope of Alkenyl Electrophiles in Pd-Catalyzed Enantioselective Cross-Coupling with 1a

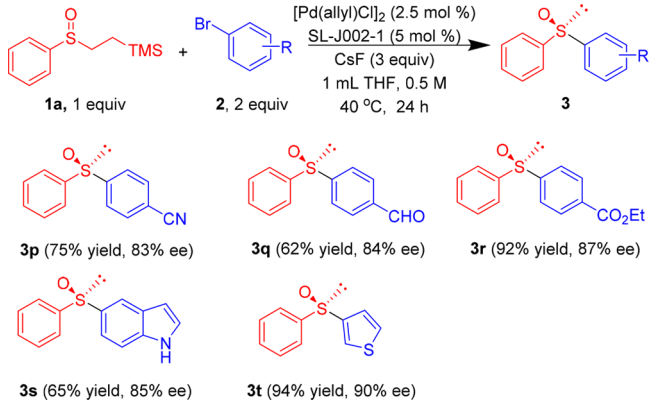


[a]One equiv 15-crown-5. [b]60 °C. [c]Two equiv of 1-cyclohexenyl trifluoromethanesulfonate was employed.

Bromo-2-butene provided the product **3n** in 88% yield and 85% ee without addition of crown ether. For reasons that are unclear, the cyclic electrophile 1-bromocyclohexene decomposed under the reaction conditions. Use of the corresponding vinyl triflate furnished the product **3o** in 44% yield and 92% ee.

Considering the mild nature of the optimized conditions, we envisioned that this system could be extended to sensitive aryl and heteroaryl bromides (Scheme 5). Aryl bromides bearing nitrile (**3p**), aldehyde (**3q**), and ester (**3r**) groups all gave moderate to high yields (75%, 62%, and 92%, respectively) with good enantioselectivities (83%−87% ee). 5-Bromoindole was also tolerated without protection of the nitrogen, providing **3s** in 65% yield with 85% ee. When 2-(trimethylsilyl)ethyl phenyl sulfoxide was coupled with 3-bromothiophene, the yield of the desired product (**3t**) was 94% with 90% ee. The absolute configuration of **3p**, **3q**, and **3r**

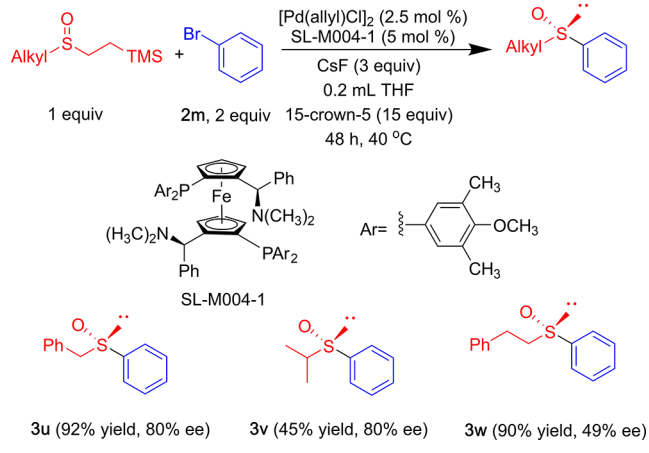
Scheme 5. Substrate Scope of Aryl Electrophiles in Pd-Catalyzed Enantioselective Cross-Coupling with 1a



were *R*, as determined by comparison of their optical rotations with reported values.[17]

The benzylic proton of an aryl benzyl sulfoxide can be deprotonated and arylated with Pd catalysts and aryl bromides under basic condition. Aryl sulfenate anions are ultimately generated.[15d] To explore the viability of our method to prepare sensitive enantioenriched sulfoxides, the benzyl sulfenate anion derived from **1j** was subjected to the reaction conditions (2.5 mol % [Pd(allyl)Cl]$_2$, 5 mol % SL-J002-1, **1j** (0.5 mmol), bromobenzene (1.0 mmol), CsF (1.5 mmol), 15-crown-5 (0.5 mmol), 0.5 mL THF at 80 °C for 24 h). The desired product was formed in 92% AY with only 45% ee. We then screened 24 different chiral phosphine ligands to improve the enantioselectivity of this substrate (see the Supporting Information for details). We found that SL-M004-1 was the best ligand, in terms of yield and enantioselectivity. When the scale increased to 0.1 mmol of **1j**, this ligand provided the desired product in 90% yield and 57% ee at 80 °C. Lowering the temperature to 40 °C gave higher enantioselectivity (73% ee); however, the yield decreased to 13%. Increasing the amount of 15-crown-5 to 15 equiv further improved the ee to 80% with an isolated yield of 92% at 40 °C (Scheme 6). Under these optimized conditions, 2-propyl-2-(trimethylsilyl)ethylsulfoxide (**1k**) and phenethyl-2-(trimethylsilyl)ethylsulfoxide (**1l**) were examined, giving **3v** (45% yield, 80% ee) and **3w** (90% yield, 49% ee). The absolute configurations of **3u** and **3w** are *S*, as determined

Scheme 6. Pd-Catalyzed Enantioselective Cross-Coupling of the Alkyl Sulfenate Anion with 2m



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by comparison of the optical rotations with the literature data.[17]

In summary, we have developed a versatile approach to synthesize a variety of enantioenriched sulfoxides from both aryl and alkyl sulfenate anions in moderate to high enantioselectivities and in good yields. This is the first catalytic asymmetric method for the generation of enantioenriched vinyl sulfoxides. Key to the success of this method is the fluoride-triggered elimination of the sulfenate anions at 40 °C, which can be captured by palladium(II) catalysts bearing an enantioenriched bidentate phosphine ligand.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03943.

Procedures, characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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