Chemical Synthesis

Research Article

Enantioselective 1,1-diarylation of terminal alkenes catalyzed by palladium with a chiral phosphoric acid

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Abstract

The enantioselective 1,1-diarylation of allyl sulfones and vinyl sulfones is reported for the first time, enabled by a combination of Pd$_2$dba$_3$ and a chiral SPINOL-derived phosphoric acid. Various chiral sulfones containing 1,1-diarylalkane motifs were obtained in moderate to good yields with moderate to high enantioselectivities. Control experiments suggested that the sulfone group plays a key role in providing enantioselectivity and reactivity control and might serve as a directing group.

Keywords: Cooperative catalysis, 1, 1-diarylation, allyl sulfone, chiral sulfone, chiral anion phase-transfer catalysis

INTRODUCTION

The chiral 1,1-diarylalkane motif is found in many bioactive natural products and pharmaceuticals [Scheme 1A][1,2]. Accordingly, much effort has been devoted to developing methods for the enantioselective synthesis of such structures[3-7]. Among the methodologies that have been devised, the transition-metal catalyzed asymmetric 1,1-diarylation of commercially available alkenes is one of the most straightforward and adjustable strategies for the synthesis of chiral compounds containing a 1,1-diarylalkane motif and has therefore attracted increasing attention[8,9]. The Sigman group first reported the enantioselective 1,1-
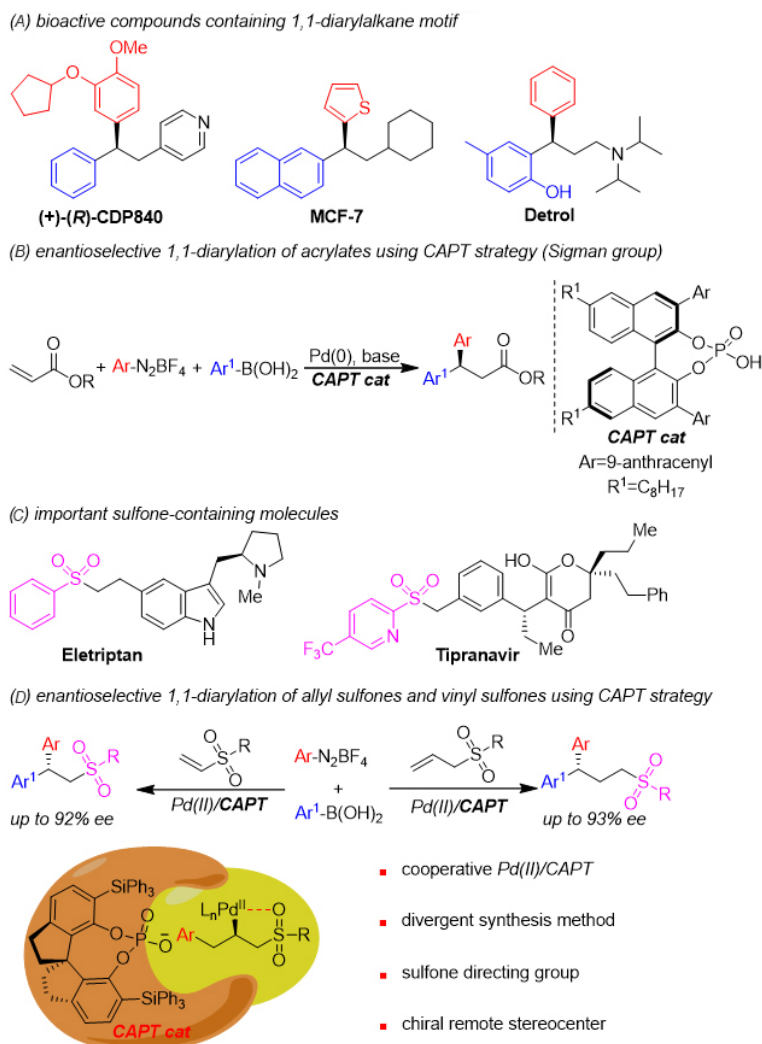
Scheme 1. Design of the enantioselective 1,1-diarylation of allyl sulfones and vinyl sulfones.

diarylation of acrylates based on a combination of palladium catalysis and chiral anion phase-transfer catalysis (*CAPT*) [Scheme 1B][10-14]. However, to the best of our knowledge, there has been no research concerning the catalytic asymmetric 1,1-diarylation of non-conjugated alkenes, which is more challenging because of the lower reactivity of these compounds and the complex requirements for regio- and enantioselectivity[15-17].

Sulfone groups are widely found in biologically active molecules [Scheme 1C][18-21]. Compounds containing these groups are also versatile synthetic intermediates because sulfones are easily transformed into a range of structurally diverse functional groups and can also function as flexible directing groups in various metal-catalyzed reactions to provide site- and enantioselective processes and control reactivity[22-26]. On this basis, we considered that sulfone groups might permit a high level of selectivity during catalytic asymmetric 1,1-diarylation. We aimed to synthesize the highly enantioselective 1,1-diarylation of allyl sulfones. This process involved two main challenges. First, allyl sulfones are less reactive than activated alkenes and so competitive reactions become more important. Examples include the traditional Heck reactions of alkene substrates and aryldiazonium salts[27-30] and the Suzuki reaction of aryldiazonium salts and arylboronic acids[16,31]. Second,
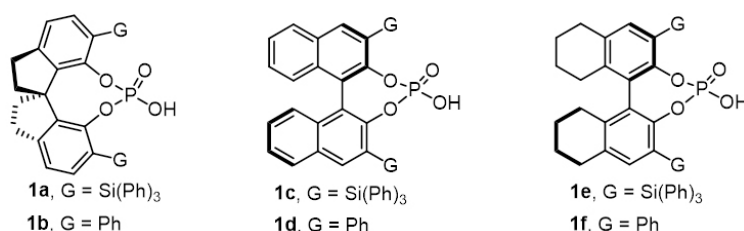
1a, G = Si(Ph)$_3$
1b, G = Ph

1c, G = Si(Ph)$_3$
1d, G = Ph

1e, G = Si(Ph)$_3$
1f, G = Ph

Figure 1. Some different chiral phosphoric acids.

the enantioselectivity control of this novel reaction process was expected to be more difficult. For these reasons, it was thought that a new catalysis system might be required. Herein, we report the highly enantioselective 1,1-diarylation of allylic sulfones using a new co-catalysis system comprising a chiral SPINOL-derived phosphoric acid and Pd$_2$dba$_3$. This methodology allows modular and direct access to chiral sulfones that contain a 1,1-diarylalkane motif and a remote stereocenter [Scheme 1D]. This new co-catalysis system was also found to be applicable to vinyl sulfones.

EXPERIMENTAL

In glovebox, **2a** (0.2 mmol), **3a** (0.2 mmol), **4a** (0.1 mmol), Pd$_2$dba$_3$ (3.7 mg, 0.004 mmol), (*R*)-**1a** (10.0 mg, 0.012 mmol), Rb$_2$CO$_3$ (69.3 mg, 0.3 mmol), anhydrous MTBE (2.0 mL) were added into an oven-dried tube (10 mL) charged with a stir bar, sealed the flask with its septum and then removed from the glovebox. The system was stirred for 48 h at 0 ºC. After the reaction was completed (monitored by TLC), the crude reaction mixture was filtered through a short silica column with PE: EA = 1:2, and the solvent was removed in vacuo. An external standard (dibromomethane) was added to the system for determining NMR yields. Product **5a** was obtained by PTLC.

RESULTS AND DISCUSSION

In our initial study, allyl sulfone **2a** was chosen as a model substrate, while 4-methoxybenzene diazonium salt **3a** and phenylboronic acid **4a** were selected as model coupling partners. A series of careful screening trials were performed (see Supplementary Materials for details). As indicated in Scheme 2 and Table 1, entry 1, the desired product **5a** was obtained in 64% yield with 96:4 er when Pd$_2$dba$_3$ and chiral SPINOL-derived phosphoric acid (*R*)-**1a** [Figure 1] were used as the catalysts in the presence of Rb$_2$CO$_3$ in methyl *tert*-butyl ether (MTBE) at 0 ºC. The use of a chiral phosphoric acid was vital to obtaining the desired reactivity and enantioselectivity during this transformation. When (*R*)-**1b** bearing a phenyl substituent was used instead of (*R*)-**1a**, **5a** was obtained in only 11% yield with 71:29 er (entry 2), with the remainder being the traditional Heck product. Replacing (*R*)-**1a** with chiral BINOL-derived phosphoric acid (*R*)-**1c** resulted in a reduction in both the yield and enantioselectivity (entry 3). It was found that the absolute configuration of product **5a** was reversed, which met the opposite axial chirality of (*R*)-BINOL **1c** and (*R*)-SPINOL **1a**. Similar results were obtained using (*R*)-**1e** (entry 5). Both lower yield and reduced enantioselectivity were observed when chiral BINOL-derived phosphoric acid (*R*)-**1d** and H$_8$-BINOL-derived (*R*)-**1f** were used (entries 4, 6) and the primary result was again the traditional Heck product. A series of different inorganic bases was subsequently examined in place of Rb$_2$CO$_3$ (entries 7-9). These trials indicated that the particular base that was used had a significant effect on the yield but only slightly modified the enantioselectivity. Using K$_2$CO$_3$ as a base gave similar results as obtained with the standard conditions, while employing Cs$_2$CO$_3$ or Na$_2$CO$_3$ led to an obvious reduction in yield. Using diethyl ether as the solvent, the enantioselectivity was lowered but not the yield (entry 10). Only a trace amount of **5a** was obtained when toluene was substituted as the solvent (entry 11). Product **5a** was obtained in 21% yield with 88:12 er when this reaction was performed at room temperature (entry 12).

Table 1. Reaction optimization[a]

Entry	Change from the "standard conditions"	Yield (%)[b]	er[c]
1	none	64	96:4
2	(R)-**1b** instead of (R)-**1a**	11	71:29
3	(R)-**1c** instead of (R)-**1a**	10	13:87
4	(R)-**1d** instead of (R)-**1a**	12	65:35
5	(R)-**1e** instead of (R)-**1a**	24	12:88
6	(R)-**1f** instead of (R)-**1a**	27	71:29
7	Cs_2CO_3 instead of Rb_2CO_3	51	96:4
8	K_2CO_3 instead of Rb_2CO_3	62	95:5
9	Na_2CO_3 instead of Rb_2CO_3	44	94:6
10	Et_2O instead of MTBE	66	90:10
11	toluene instead of MTBE	trace	-
12	rt instead of 0 ºC	21	88:12

[a]Unless otherwise noted, the reaction was conducted with **2a** (0.2 mmol), **3a** (0.2 mmol), **4a** (0.1 mmol), Rb_2CO_3 (0.3 mmol), (R)-**1a** (0.012 mmol) and Pd_2dba_3 (0.004 mmol) in MTBE (2 mL) at 0 ºC for 48 h under Ar. [b]Isolated yields. [c]All er values were determined by SFC.
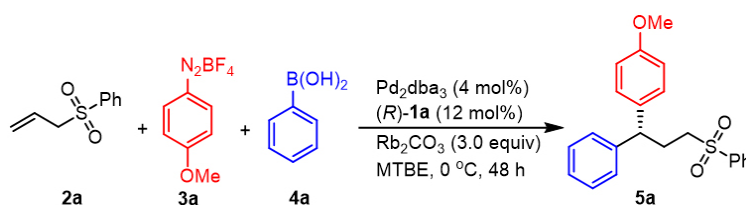
Scheme 2. The standard conditions of the catalytic asymmetric 1,1-diarylation of allylic sulfone.

Taking advantage of the optimized conditions, the reaction scope was first examined with a variety of arylboronic acids. In general, all arylboronic acids gave the desired product in a moderate yield with moderate to high levels of enantioselectivity [Scheme 3]. We found that the presence of methyl or fluorine groups at the 4-position of the phenyl ring slightly affected the yield and enantioselectivity, while electron-deficient substituents such as chlorine, ester and trifluoromethyl groups resulted in decreased yields and enantioselectivities (**5b**-**5f**). The reaction was also found to proceed with (4-hydroxyphenyl) boronic acid, giving the desired product **5g** in 96.5:3.5 er, albeit with a yield of 27%. Following these trials, phenylboronic acids bearing *meta* substituents such as methoxy and methyl groups were also applied to this reaction, and the corresponding products were obtained with moderate yields and high enantioselectivities (**5h**-**5i**). Interestingly, *ortho*-tolylboronic acid also worked well in this protocol, yielding product **5j** in 62% yield and 96:4 er. A multi-substituted phenylboronic acid was applied to this system and provided product **5k** with a high level of enantioselectivity. Naphthalen-2-ylboronic acid was also a suitable coupling partner and delivered product **5l** in 53% yield with 95.5:4.5 er. It is worth noting that a series of (heter)arylboronic acids were also examined in this reaction. In these trials, product **5m** was obtained in 60% yield with 86.5:13.5 er, while products **5n** and **5o** were generated in lower yields with moderate enantioselectivities (More results about (hetero)arylboronic acids, please see SI). Following the experiments described above, the reaction scope was examined by assessing different aryldiazonium salts (**5p**-**5s**). Changing the substituent of the model coupling partner **3a** from a methoxy to a benzyloxy group maintained high enantioselectivity and also gave a moderate yield. It should be noted that the absolute configuration of **5p** was assigned by X-ray crystallography[32]. It was also determined that the *meta*-methoxybenzene diazonium salt was compatible with this reaction, giving product **5q** with 40% yield and 95.5:4.5 er. In addition, using ethyl ether as the
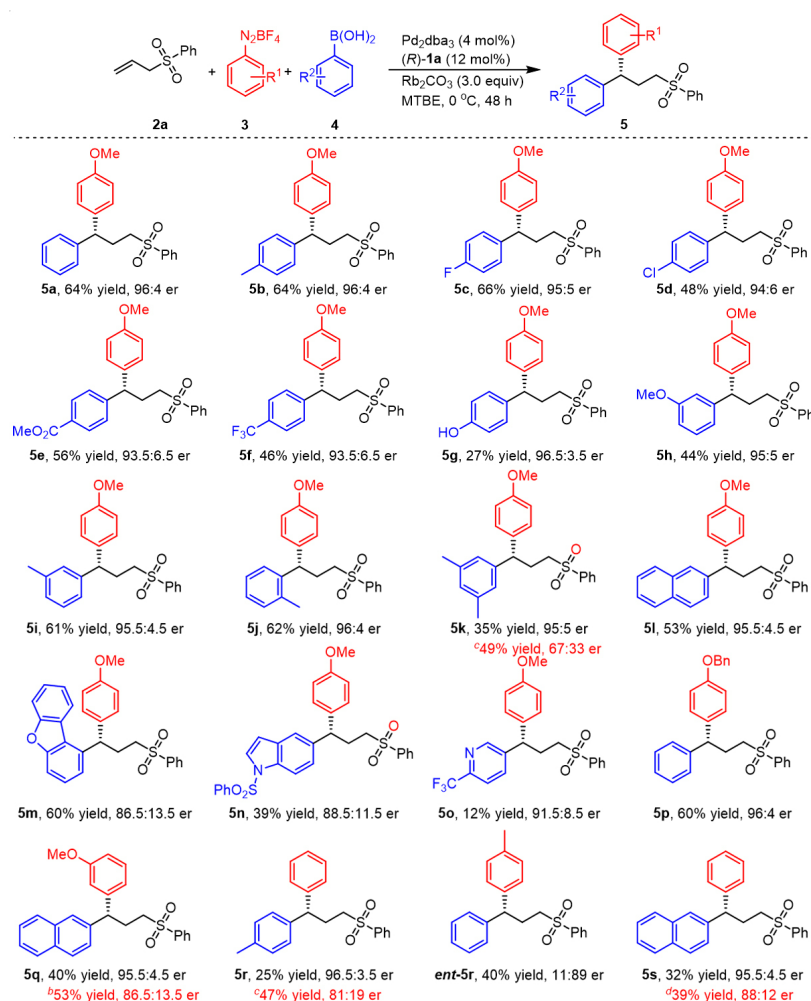
Scheme 3. Scope of arylboronic acids and aryldiazonium salts[a]. [a]Unless otherwise noted, the reaction was conducted with **2a** (0.2 mmol), **3** (0.2 mmol), **4** (0.1 mmol), Rb$_2$CO$_3$ (0.3 mmol), (R)-**1a** (0.012 mmol) and Pd$_2$dba$_3$ (0.004 mmol) in MTBE (2 mL) at 0 °C for 48 h under Ar. Isolated yields are shown. The er values were determined by SFC. [b]Et$_2$O was used instead of MTBE as the solvent. [c]Guanidine carbonate was used instead of Rb$_2$CO$_3$. [d]Guanidine carbonate (1.0 equiv) and Rb$_2$CO$_3$ (1.0 equiv) were used instead.

solvent, product **5q** was produced in 53% yield with a lower er value. In further trials, *para*-tolylboronic acid and naphthalen-2-ylboronic acid were employed as coupling partners, and the corresponding products **5r** and **5s** were generated in moderate yields with good enantioselectivities. As expected, when the phenyl diazonium salt and 4-methylboronic acid were used as coupling partners, product *ent*-**5r** was obtained in 40% yield with 11:89 er. These results indicate that the range of aryldiazonium salts applicable to this process is relatively limited.

To further extend the scope of this reaction, we subsequently explored various allyl sulfone substrates [Scheme 4]. The steric effects of phenyl ring substituents were initially examined. A methyl group at the 4-position of the phenyl moiety was found not to affect the yield or enantioselectivity, while a tertiary butyl group decreased the yield (**5t-5u**). The electronic effect of substituents was also evaluated. Both an electron-rich methoxy substituent and electron-poor substituents such as fluorine, ester and trifluoromethyl groups slightly decreased the yield and enantioselectivity (**5v-5y**). Substrates bearing *meta*-methoxy-phenyl, 3,5-dichlorophenyl and 1-naphthyl moieties were also examined. In each case, the corresponding product was obtained with moderate efficiency and a high level of enantioselectivity (**5z-5ab**). However, a substrate with
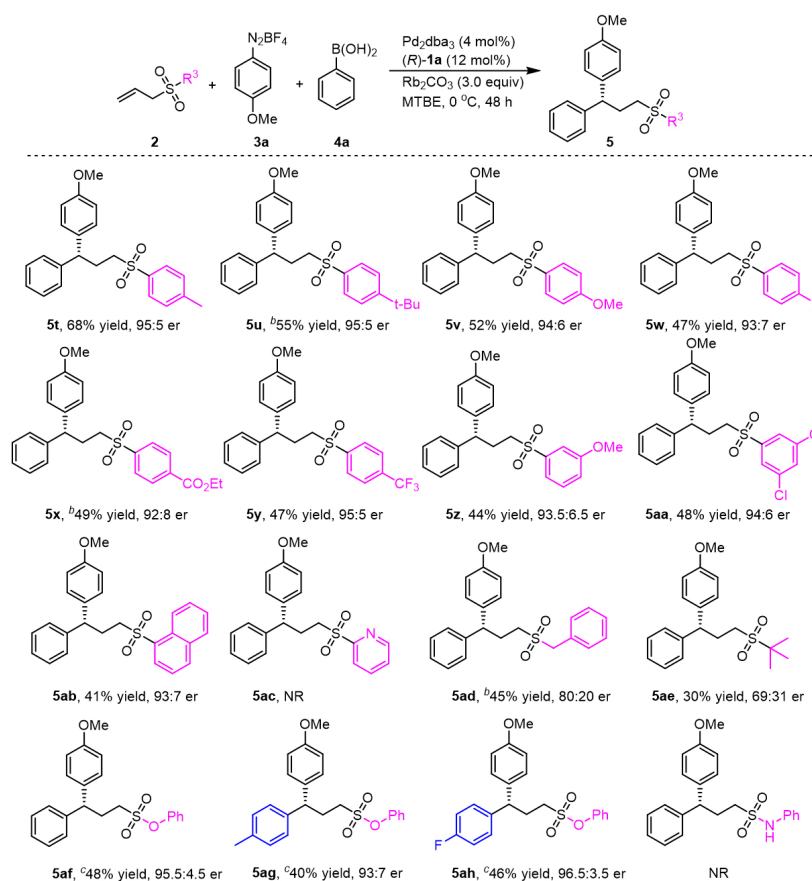
Scheme 4. Scope of allylic sulfones [a]. [a]Unless otherwise noted, the reaction was conducted with **2** (0.2 mmol), **3a** (0.2 mmol), **4a** (0.1 mmol), Rb$_2$CO$_3$ (0.3 mmol), (*R*)-**1a** (0.012 mmol) and Pd$_2$dba$_3$ (0.004 mmol) in MTBE (2 mL) at 0 °C for 48 h under Ar. Isolated yields are shown. The er values were determined by SFC. [b]The reaction was performed at 10 °C. [c]Cs$_2$CO$_3$ was used instead of Rb$_2$CO$_3$.

a SO$_2$Py group did not give the desired product (**5ac**), presumably because the pyridine group strongly coordinated with the palladium to suppress the reaction. Additionally, the use of alkyl groups, such as benzyl and tertiary butyl groups, instead of the phenyl group resulted in significant decreases in yield and enantioselectivity (**5ad**-**5ae**). From these data, it is evident that the sulfone group was a vital aspect of obtaining enantioselectivity and reactivity control. To our delight, allyl sulfonates were also suitable for this reaction. The products **5af**-**5ah** were always obtained in moderate yields with high enantioselectivities. As expected, allyl sulfonamide suppressed the transformation.

Because chiral β,β-diaryl sulfones can be readily transformed into bioactive pharmaceutical molecules such as (*R*)-CDP-840 and (*R*)-MCF-7[33,34], the extension of this catalytic system to the 1,1-diarylation of vinyl sulfones was investigated. The desired product **7a** was obtained in a 67% yield and with 95:5 er from the reaction of vinyl sulfone **6a**, 4-methoxybenzene diazonium salt **3a** and phenylboronic acid **4a**, using Cs$_2$CO$_3$ instead of Rb$_2$CO$_3$ [Scheme 5]. Following this, a number of arylboronic acids were applied to the reaction and the corresponding products were obtained in moderate yields with high enantioselectivities (**7b**-**7f**). It is of note that *ortho*-tolylboronic acid was also suitable for this protocol and gave product **7e** in 45% yield and 96:4 er. Phenyl aryldiazonium salt was employed in this reaction and product **7g** was obtained in 45% yield and 93.5:6.5 er. The absolute configuration of (*S*)-**7g** was determined by comparison with optical rotation data for the reported literature[26]. Likewise, the product **7h** was obtained in 30% yield with 96:4 er using vinyl sulfonate as the substrate. Finally, product *ent*-**7a** was produced in moderate yield with good
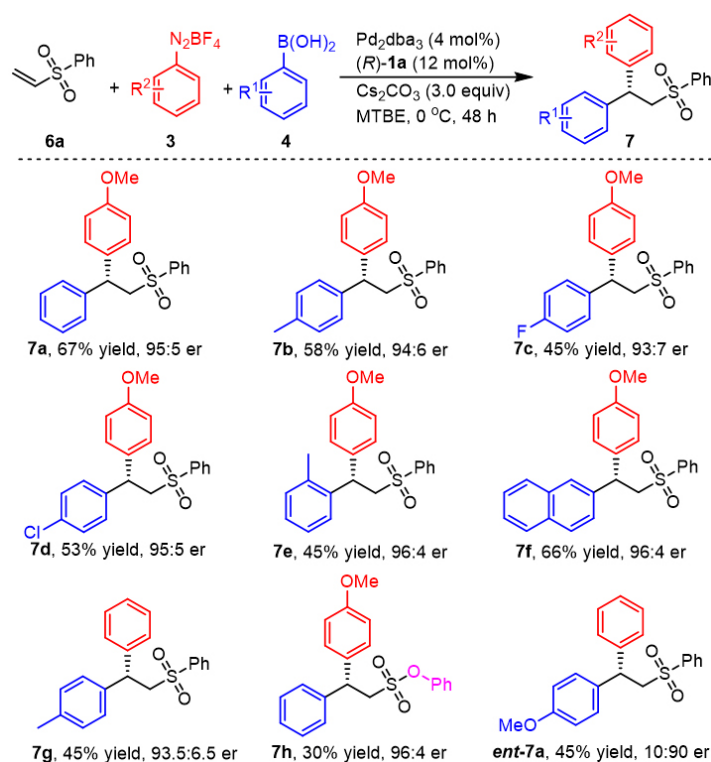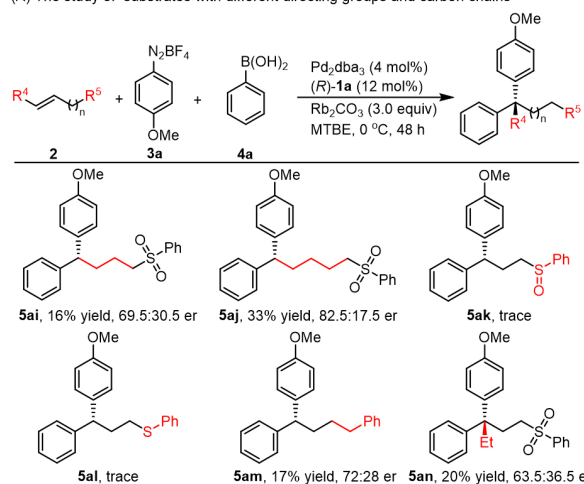
Scheme 5. Scopes of arylboronic acids and aryldiazonium salts[a]. [a]Unless otherwise noted, the reaction was conducted with **6a** (0.2 mmol), **3** (0.2 mmol), **4** (0.1 mmol), Cs$_2$CO$_3$ (0.3 mmol), (*R*)-**1a** (0.012 mmol) and Pd$_2$dba$_3$ (0.004 mmol) in MTBE (2 mL) at 0 ºC for 48 h under Ar. Isolated yields are shown. The er values were determined by SFC.

enantioselectivity.

The origin of the high enantioselectivities obtained from this reaction and the effect of the sulfone group were explored by carrying out the reaction using several different substrates [Scheme 6A]. These trials showed that increasing the length of the carbon chain between the sulfone group and the double bond greatly affected the yield and enantioselectivity (**5ai**-**5aj**). The reaction was also inhibited upon changing from a sulfone group to either a sulfoxide or thioether group (**5ak**, **5al**). Additionally, the reaction was suppressed after substituting a sulfoxide or thioether group for the sulfone (**5ak**, **5al**), possibly because of the strong coordination effects of the sulfoxide and thioether groups. When but-3-en-1-ylbenzene was used instead of **2a**, product **5am** was only obtained in 17% yield and 72:28 er. On the basis of these results, we suggest that the sulfone moiety serves as a directing group during this reaction. An internal alkene substrate was also tested, and the desired product **5an**, bearing a quaternary carbon center, was obtained in only a 20% yield with just a 63.5:36.5 er value. Thus, a terminal double bond is essential for high enantioselectivity. The effects of the boronic acid group on the reactivity and enantioselectivity of this process were first assessed by using esterified phenylboronic acid **9a** instead of phenylboronic acid and no desired product **5a** was obtained [Scheme 6B]. Product **5a** was obtained in 37% yield with 88:12 er [Scheme 6C]. The negative results established that the standard boronic acid group was crucial to this reaction. The use of Pd(OAc)$_2$ instead of Pd$_2$dba$_3$ as the catalyst afforded the desired product **5a** with 96:4 er, suggesting that the dba moieties did not participate in the asymmetric catalytic reaction [Scheme 6D]. Because the mass balance was the traditional Heck product **8a** in this transformation, this compound was employed as the starting material in a subsequent trial with the standard reaction conditions. The desired product **5a** was not obtained [Scheme 6E]. As shown in Scheme 6F, a cross-over experiment was further performed, but no

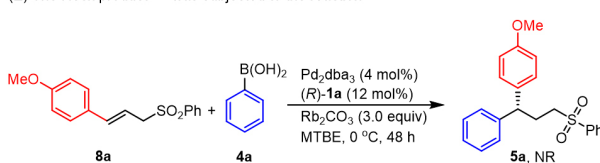(A) The study of substrates with different directing groups and carbon chains

5ai, 16% yield, 69.5:30.5 er

5aj, 33% yield, 82.5:17.5 er

5ak, trace

5al, trace

5am, 17% yield, 72:28 er

5an, 20% yield, 63.5:36.5 er

(B) (4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzene **9a** was used instead of phenylboronic acid **4a**

5a, NR
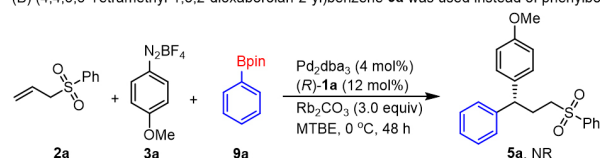
(C) Tributyl-phenyl-stannane **10a** was used instead of phenylboronic acid **4a**

5a, 37% yield, 88:12 er
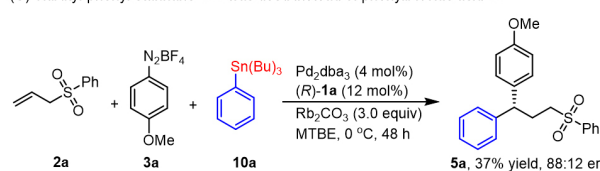
(D) Pd(OAc)$_2$ was used instead of Pd$_2$dba$_3$

5a, 29% yield, 96:4 er
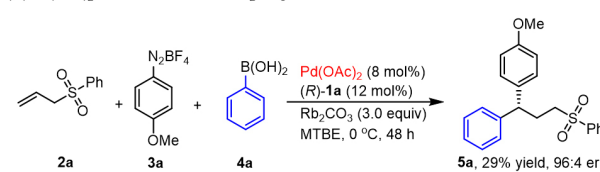
(E) The Heck product **8a** was subjected to the reaction

5a, NR

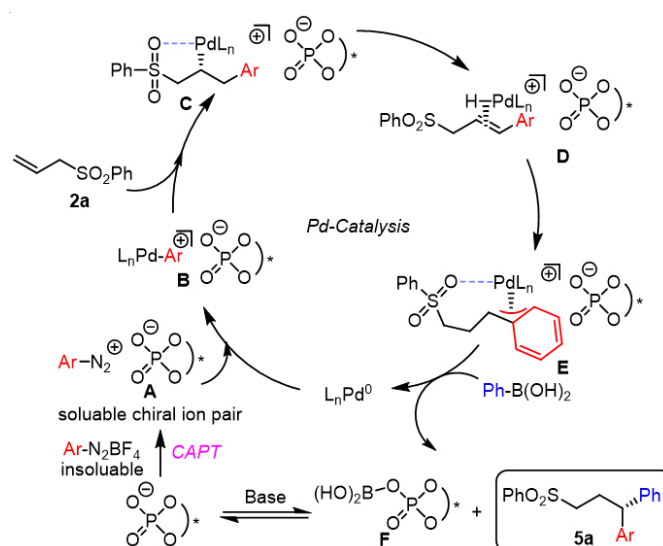(F) The cross-over experiment

5a, 37% ^{1}H NMR yield

cross-over product, Not detected
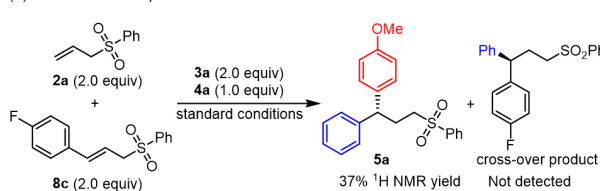
Scheme 6. Mechanistic studies.

cross-over product was obtained. Based on these observations, we believe that the Heck product was unable to participate in subsequent reactions with the arylboronic acid to form the 1,1-diarylation product.

Scheme 7. Proposed catalytic cycle. CAPT: Chiral anion phase-transfer catalysis.

Based on these experimental results and previous work[10], a possible mechanism for the catalytic cycle was devised [Scheme 7]. In this mechanism, soluble chiral ion pair **A** is first generated from a chiral phosphate anion and the insoluble tetrafluoroborate aryldiazonium salt in the presence of Rb_2CO_3. Cationic Pd-aryl intermediate **B** is then formed via the oxidative addition of **A** in conjunction with Pd_2dba_3 and subsequently undergoes an enantioselective migratory insertion of **2a** to form intermediate **C**. Intermediate **E** is generated from **C** through β-hydride elimination and reinsertion. Finally, **E** reacts with phenylboronic acid **4a**, followed by reductive elimination, forming 1,1-diarylation product **5a**.

CONCLUSION

In conclusion, this work demonstrated the enantioselective 1,1-diarylation of allyl sulfones using a cooperative strategy based on a chiral SPINOL-derived phosphoric acid and Pd_2dba_3. This newly developed cooperative catalysis was also applied to the asymmetric 1,1-diarylation of vinyl sulfones. This catalytic system allows for the rapid construction of a variety of chiral sulfones containing a 1,1-diarylalkane motif and a remote stereocenter. Interestingly, we discovered that the sulfone group can function as a directing group and is important for achieving enantioselectivity and reactivity control. The investigation of detailed mechanisms and cooperative catalysis as a means of synthesizing other useful compounds is ongoing in our laboratory.

DECLARATIONS

Authors' contributions
Designing the experiments, writing the manuscript, and being responsible for the whole work: Chen ZM
Performing the experiments: Ji K, Huang J
Synthesizing the substrates: Ji K, Huang J, Zhang XY

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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32. CCDC 2152365 (**5p**) contains the supplementary crystallographic data for this paper. More detail, see supporting information chapter 6. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre. Available from: www.ccdc.cam.ac.uk/structures [Last accessed on 12 Oct 2022].

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