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Palladium/PC-Phos–Catalyzed Enantioselective Arylation of General Sulfenate Anions: Scope and Synthetic Applications

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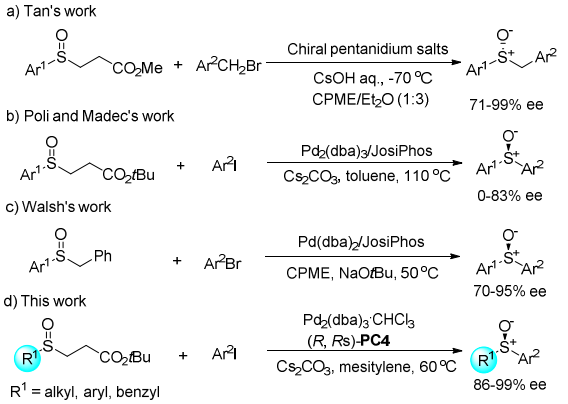
ABSTRACT: Herein we reported an efficient palladium catalyzed enantioselective arylation of both alkyl and aryl sulfenate anions to deliver various chiral sulfoxides in good yields (up to 98%) with excellent enantioselectivities (up to 99% ee) by the use of our developed chiral O, P-ligands (**PC-Phos**). PC-Phos are easily prepared in short steps from inexpensive commercially available starting materials. The single crystal structure of the **PC4**/$PdCl_2$ showed that a rarely observed eleven-membered ring was formed via the O, P-coordination with the palladium (II) center. The salient features of this method include general substrate scope, ease of scale-up, applicable to the late-stage modification of bioactive compounds and the synthesis of a marketed medicine Sulindac.

INTRODUCTION

Chiral sulfoxides are prevalent in natural products, medicinal chemistry, and marketed pharmaceutics such as esomeprazole and Provigil.[1] They are also widely used as chiral auxiliaries, chiral ligands and organocatalysts in asymmetric synthesis.[2] In general, enantioenriched sulfoxides are prepared via two main classical approaches including the nucleophilic substitution of nonracemic sulfinate amides or esters using organometallic reagents and the direct asymmetric sulfide oxidation. The nucleophilic substitution approach was pioneered by Andersen in 1962. Afterwards, this method has been greatly improved by the variants of Andersen's method. They still suffer from a lack of generality and functional group tolerance because of the use of reactive lithium- or magnesium-based nucleophiles.[3] On the other hand, the major breakthrough was made in the metal-catalyzed asymmetric direct oxidation of prochiral sulfides in 1984 by Kagan and Modena based on the Sharpless asymmetric epoxidation procedure.[4] Despite several catalytic systems based on other elegant metals have been developed for the asymmetric sulfide oxidation reactions, the drawbacks of these methods including strong oxidizing reagents limiting their functional group compatibility and the issue of over-oxidation to sulfone was not well addressed.[5] Thus, the development of efficient and general method for the enantioselective synthesis of sulfoxides is still highly desirable.

Recently, the alkylation of *in-situ* generated sulfenate anions has emerged as an alternative approach to achieve enantioenriched sulfoxides, which was pioneered by Perrio and co-workers.[6] Later, Tan and co-workers developed a novel chiral halogenated pentanidium salts to achieve the highly enantioselective benzylation of sulfenate anions, furnishing various benzyl aryl sulfoxides in 71-99% ee (Scheme 1a).[7] Despite the fact that transition metal-catalyzed arylation of sulfenate anions (RSO^-) synthesis of racemic sulfoxides have been well developed,[8] the asymmetric version of this type reaction for the enantioselective synthesis of sulfoxides has been rarely explored. In 2007, Poli, Madec, and co-workers firstly reported the palladium-catalyzed enantioselective arylation of sulfenate anions to afford chiral sulfoxides with 0-83% ee (Scheme 1b).[9] Very recently, after systematic screening of 192 different types of commercially available chiral ligands, Walsh and co-workers successfully realized such a nice palladium-catalyzed asymmetric arylation of aryl sulfenate anions to achieve chiral diaryl sulfoxides with 70-95% ee (Scheme 1c).[10]

Scheme 1. Enantioselective synthesis of sulfoxides based on sulfenate anions.



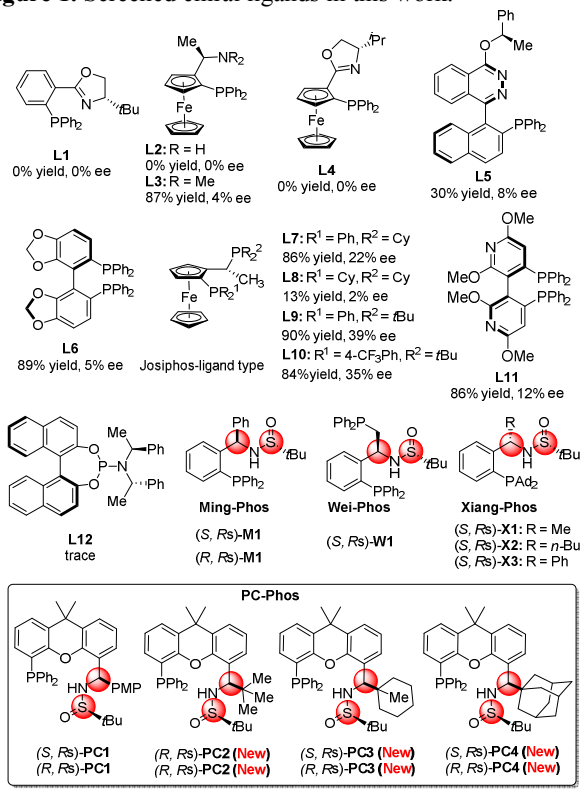
Remarkably, the same group reported the first general arylation of alkyl sulfenate anions with aryl halides to generate racemic alkyl substituted sulfoxides.[8g] However, only two examples of palladium–catalyzed enantioselective arylation of benzyl sulfenate anions were reported with low ee values (up to 47% ee).[9a] Despite these significant advances, there is still lack of a general robust catalyst system for enantioselective arylation of both aryl and alkyl sulfenate anions for the efficient synthesis of not only diaryl sulfoxides but also aryl alkyl sulfoxides. Herein, we report an efficient palladium/PC-Phos catalyst system, which are the first robust catalyst system for the enantioselective arylation of alkyl sulfenate anions as well as aryl sulfenate anions to deliver chiral diaryl or aryl alkyl sulfoxides in good yields (up to 98%) with up to 99% ee (Scheme 1d).

RESULT AND DISSCUSION.

Optimization of Reaction Conditions. We began our study by choosing *tert*-butyl 3-(benzylsulfinyl)propanoate **1a** and iodobenzene **2a** as the model substrates (Table 1). A series of commercially available various types of chiral ligands such as

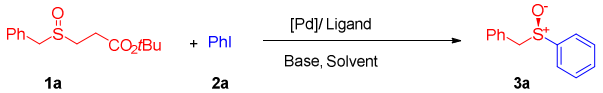
bidentate N,P-ligands **L1-L5**, P,P-ligands (*R*)-BINAP, (*R*)-Segphos(**L6**), Josiphos (**L7-L10**), and **L11,** as well as monodendate Binol-derived phosphoramidite **L12** were firstly tested (Figure 1, for additional details, please see SI), unfortunately less than 40% ee was obtained, indicating the asymmetric arylation of alkyl sulfenate anions (RSO-) is indeed much more challenging than the synthesis of diaryl sulfoxides by the cross-coupling reaction. Recently, we developed a series of chiral sulfinamide phosphine ligands and found that these new type of ligands could act either as monodentated ligand in gold–catalysis or O, P-ligand in copper-catalysis.[11] Disappointingly, Ming-Phoses (*R*, *Rs*)-**M1**, (*S*, *Rs*)-**M1** and Wei-Phos (*S*, *Rs*)-**W1** were found to be inefficient in this palladium-catalyzed enantioselective arylation of alkyl sulfenate anion (Table 1 entries 1-3). Then Xiang-Phoses (*S*, *Rs*)-**X1**, (*S*, *Rs*)-**X2** and (*S*, *Rs*)-**X3** with more sterically bulky 1-adamantyl substituent on the P atom were tested, and the desired sulfoxide product was obtained in low yield and low ee (Table 1 entries 4-6).

Figure 1. Screened chiral ligands in this work.



With the fact that XantPhos is the best ligand for the racemic reaction,[8a,b,f] and our recently developed PC-Phos[12] sharing a same Xanthene skeleton, we next focused on the examination of PC-phos. Gratifyingly, the reaction could give **3a** in 26% yield with 29% ee, when the (*R*, *Rs*)-**PC1** was used as the chiral ligand (Table 1, entry 8). To modified ligands **PC2**–**PC4**, the desired sulfoxide product **3a** could be isolated in 71% yield with 38% ee with the use of (*S*, *Rs*)-**PC2**. In contrast, replacing (*S*, *Rs*)-**PC2** with its diastereomer (*R*, *Rs*)-**PC2** significantly improved the ee from 38% to 91% (Table 1, entry 10). Further increasing the steric hindrance of the ligand, structured as **PC3** with 1-methylcyclohexyl allows the formation of **3a** with an increased yield (84%) and a slightly better enantioselectivity (Table 1, entries 11-12). Next, (*S*, *Rs*)-**PC4** and (*R*, *Rs*)-**PC4** with bulkier 1-adamantyl group were investigated, and 79% yield of the product with 94% ee could be delivered with using of (*R*, *Rs*)-**PC4** (Table 1, entries 13-14). Moreover, 96% ee and 83% yield were obtained, when lowering the reaction temperature from 80 °C to 60 °C with elongated reaction time (Table 1, entry 15). However, further screening of conditions including bases, palladium sources and solvents could not bring better results (for additional details, please see SI).

Table 1. Optimization of reaction conditions.[a]



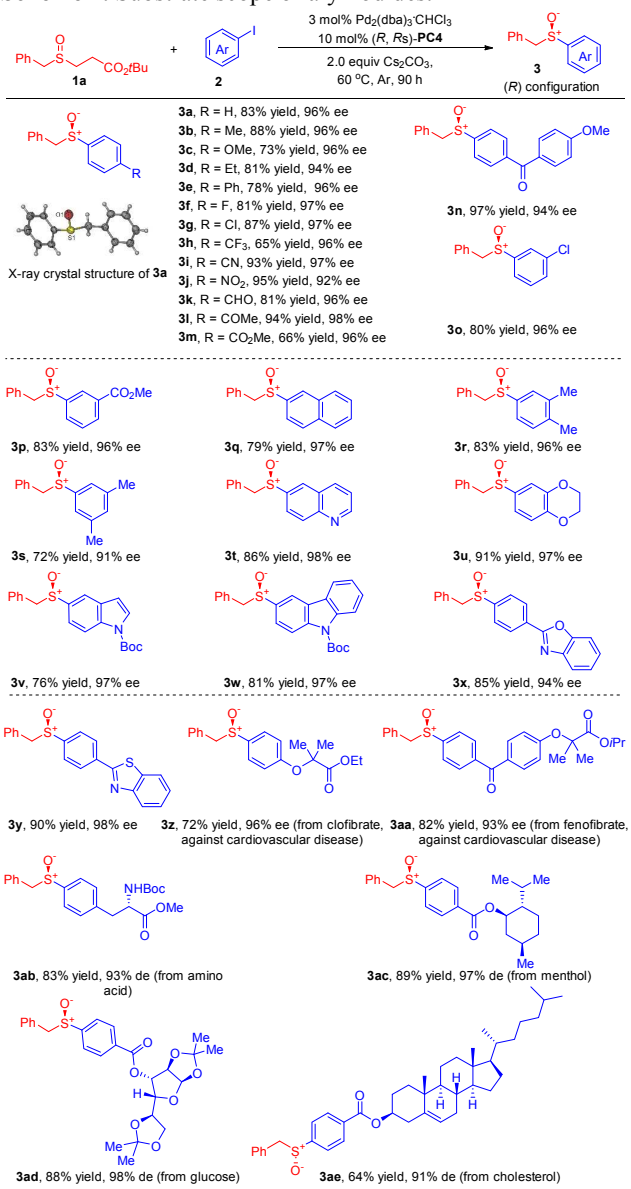
Entry	Ligand	Pd sources	Base	Yield[b](Ee[c])(%)
1	(*R*, *Rs*)-**M1**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	0 (-)
2	(*S*, *Rs*)-**M1**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	0 (-)
3	(*S*, *Rs*)-**W1**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	trace (-)
4	(*S*, *Rs*)-**X1**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	18 (26)
5	(*S*, *Rs*)-**X2**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	15 (30)
6	(*S*, *Rs*)-**X3**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	13 (65)
7	(*S*, *Rs*)-**PC1**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	trace (-)
8	(*R*, *Rs*)-**PC1**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	26 (29)
9	(*S*, *Rs*)-**PC2**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	71 (38)
10	(*R*, *Rs*)-**PC2**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	78 (91)
11	(*S*, *Rs*)-**PC3**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	70 (47)
12	(*R*, *Rs*)-**PC3**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	84 (92)
13	(*S*, *Rs*)-**PC4**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	76 (40)
14	(*R*, *Rs*)-**PC4**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	79 (94)
15[d]	(*R*, *Rs*)-**PC4**	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	83 (96)
16[d,e]	(*R*, *Rs*)-**PC4**	$PdCl_2$	Cs_2CO_3	67 (92)
17[d,e]	(*R*, *Rs*)-**PC4**	$Pd(OAc)_2$	Cs_2CO_3	64 (94)
18[d,e]	(*R*, *Rs*)-**PC4**	$Pd_2(dba)_3$	Cs_2CO_3	63 (95)
19[d,e]	(*R*, *Rs*)-**PC4**	$[Pd(C_3H_5)Cl]_2$	Cs_2CO_3	74 (84)
20[d,e]	(*R*, *Rs*)-**PC4**	$Pd(CH_3CN)_2Cl_2$	Cs_2CO_3	67 (92)
21[d]	(*R*, *Rs*)-**PC4**	$Pd_2(dba)_3{\cdot}CHCl_3$	Na_2CO_3	trace (-)
22[d]	(*R*, *Rs*)-**PC4**	$Pd_2(dba)_3{\cdot}CHCl_3$	K_2CO_3	60 (96)
23[d]	(*R*, *Rs*)-**PC4**	$Pd_2(dba)_3{\cdot}CHCl_3$	NaOH	trace (-)

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), Cs_2CO_3 (2.0 equiv), 3 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, and 10 mol% ligand in 2.0 mL mesitylene, 80 °C under Ar for 48 h. [b]Isolated yield. [c]Ee was determined by HPLC analysis [d]60 °C under Ar for 90 h. [e]5 mol % palladium catalysts.

Enantioselective Arylation of Benzyl Sulfenate Anions. We then explored the substrate scope of aryl iodides with sulfoxide **1a** (Scheme 2). A variety of aryl iodides bearing electron-donating substituents were successfully converted to the desired products **3a-3e** in high yields with excellent enantioselectivities (94-96% ee). The absolute configuration of **3a** was confirmed by X-ray crystallography. Aryl iodides with electron-withdrawing groups such as chloro, fluoro, nitro, cyano, formyl, esters, trifluoromethyl as well as ketones were good reaction partners and afforded the corresponding substituted phenyl benzyl sulfoxides **3f-3p** in 65-97% yields with excellent enantioselectivities (92-98% ee). Moreover, disubstituted aryl iodides also reacted smoothly to furnish the arylation products **3r-3s** in good to excellent yields with 91-96% ee. Heteroaryl sulfoxides could exhibit anticancer, antifungal and anti-inflammatory activities.[1b,c,h,j] Fortunately, a variety of heteroaryl iodides, in particular, indole-, quinoline-, carbazole-

, benzooxazole- and benzothiazole containing substrates were successfully compatible with the arylation conditions (**3t-3y**, 94-98% ee). Disappointingly, iodopyridines and ortho-substituted aryl halides did not work well under the reaction conditions.

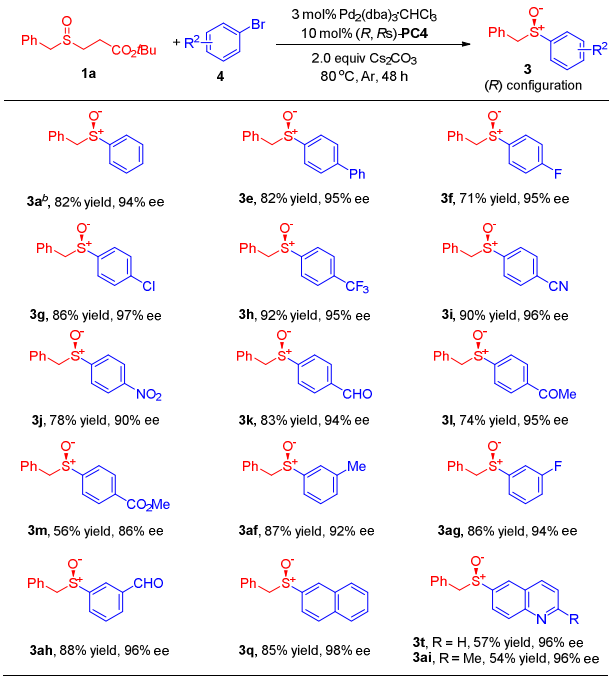
Scheme 2. Substrate scope of aryl iodides.[a]



[a]Unless otherwise noted, all reactions were carried out with 0.2 mmol of **1a**, 0.6 mmol of **2**, Cs_2CO_3 (2.0 equiv), 3 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, and 10 mol% ligand in 2.0 mL of mesitylene, 60 °C under Ar for 90 h.

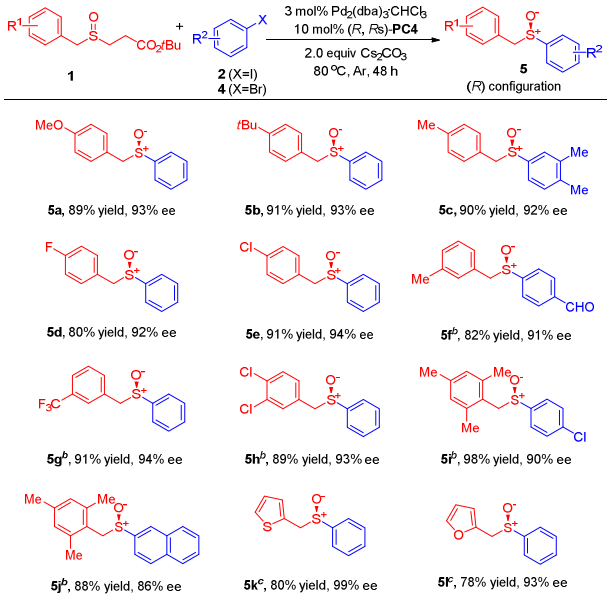
To demonstrate potential applications, late-stage modification of various natural products, biologically active molecules and pharmaceuticals derivatives were conducted. clofibrate derivative **3z** and fenofibrate derivative **3aa** could be obtained in 72% yield, 96% ee and 82% yield, 93% ee, respectively. Menthol, carbohydrate, cholesterol and amino acid derived chiral sulfoxides **3ab-3ae** were isolated in good yields and high diastereoselectivities.

Scheme 3. Substrate scope of aryl bromides.[a]



[a]Unless otherwise noted, all reactions were carried out with 0.2 mmol of **1a**, 0.6 mmol of **4**, Cs_2CO_3 (2.0 equiv), 3 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, and 10 mol% ligand in 2.0 mL mesitylene, 80 °C under Ar for 48 h. [b]56 h.

Scheme 4. Substrate scope of benzyl sulfenates.[a]

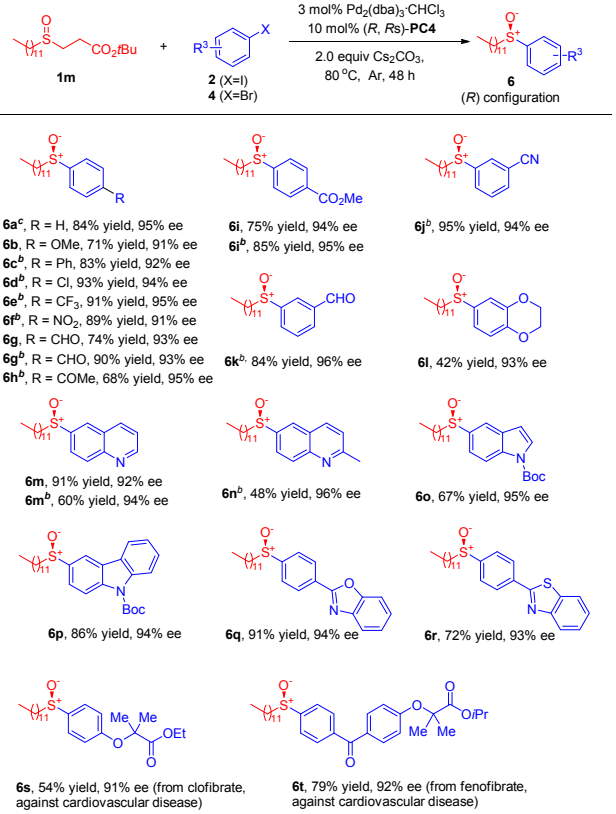


[a]Unless otherwise noted, all reactions were carried out with 0.2 mmol of **1**, 0.6 mmol of **2** or **4**, Cs_2CO_3 (2.0 equiv), 3 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, and 10 mol% ligand in 2.0 mL of mesitylene, 80 °C under Ar for 48 h. [b] Use aryl bromides. [c]60 °C under Ar for 90 h.

Various aryl bromides were also well applicable to this transformation to give the desired chiral aryl benzyl sulfoxides in high ee even though the reactions were run at higher temperature (Scheme 3). We next turned to examine the scope of benzyl sulfenate anions (Scheme 4). Both electron-donating and electron-withdrawing group substituted benzyl sulfenate worked well to deliver the corresponding aryl benzyl sulfoxides in good to excellent yields with good levels of enantioselectivities (**5a-5g**, 91-94% ee). Moreover, the steric hindrance had little effect on this transformation, as evidenced by the

high yields with 86-93% enantioselectivities of **5h-5j**. Importantly, heterocycle-substituted benzyl sulfoxides such as 2-furanyl and 2-thienyl derivatives could also act as cross-coupling partners, furnishing **5k-5l** in 78-80% yields with 93-99% ee.

Scheme 5. Examination the scope of aryl halides in the arylation of alkyl sulfenate anion.[a]

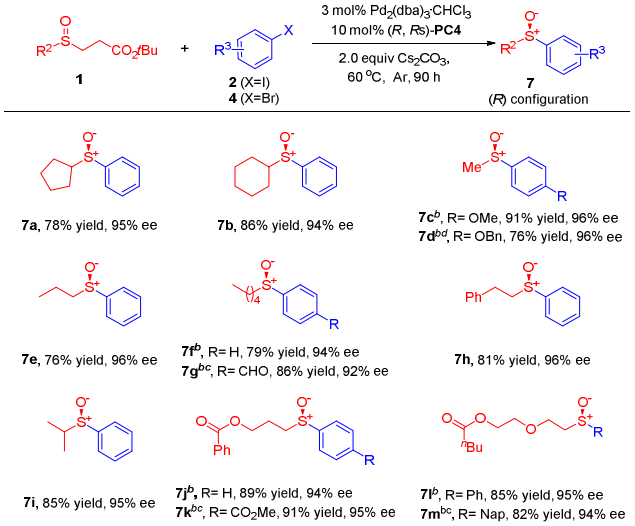


[a]Unless otherwise noted, all reactions were carried out with 0.2 mmol of **1m**, 0.6 mmol of **2** or **4**, Cs_2CO_3 (2.0 equiv), 3 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, and 10 mol% ligand in 2.0 mL mesitylene, 80 °C under Ar for 48 h. [b] Use aryl bromides [c]60 °C under Ar for 90 h.

Enantioselective Arylation of Alkyl Sulfenate Anions. Inspired by the good substrate scope of benzyl sulfenate anions and aryl halides, we then examine the scope of aryl halides in the cross-coupling with alkyl sulfenate anions (Scheme 5). Electron-neutral, -donating and -withdrawing substituents were generally well-tolerated, a□ording the desired products **6a-6k** in good yields with excellent enantioselectivities. Moreover, a range of heteroaryl halides also led to moderate yields and excellent enantioselectivities (**6l-6r**, 92-96% ee). Particularly, the substrates with a substituent derived from clofibrate derivative and fenofibrate, the desired products **6s** and **6t** were also observed in moderate yields with excellent enantioselectivities (91-92% ee).

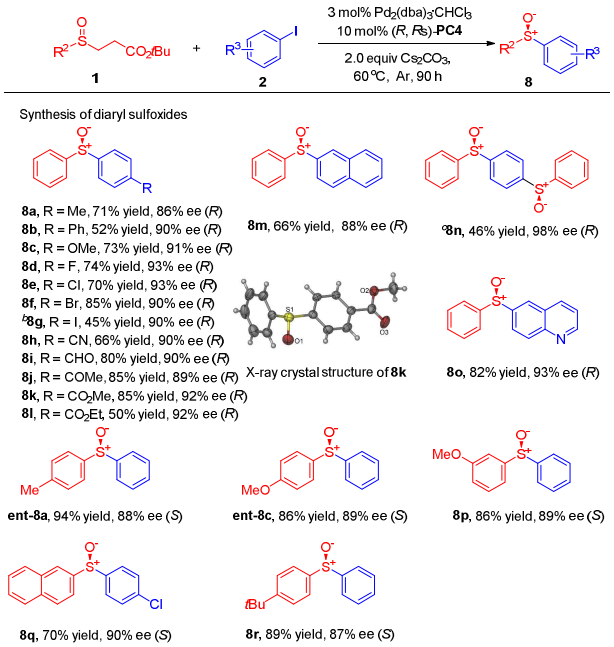
A variety of cyclic, linear or branched alkyl sulfenate anions were then investigated under the standard conditions (Scheme 6). The corresponding sulfoxides **7a-7i** were could be obtained in 76-86% yields with 92−96% ee. Functionalized alkyl sulfenate anions could be also as the cross-coupling partner with aryl halides to deliver the corresponding products **7j-7m** in excellent yields (82-91%) and enantioselectivities (94-95% ee).

Scheme 6. Substrate scope of alkyl sulfenates[a]



[a]Unless otherwise noted, all reactions were carried out with 0.2 mmol of **1**, 0.6 mmol of **2** or **4**, Cs_2CO_3 (2.0 equiv), 3 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, and 10 mol% ligand in 2.0 mL mesitylene, 60 °C under Ar for 90 h. [b]80 °C under Ar for 48 h. [c]Use aryl bromides. [d]3 mmol scale of reaction.

Scheme 7. enantioselective synthesis of diaryl sulfoxides.[a]

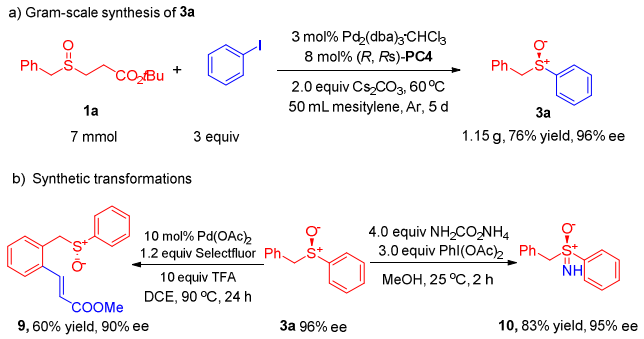


[a]Unless otherwise noted, all reactions were carried out with 0.2 mmol of **1**, 0.6 mmol of **2**, Cs_2CO_3 (2.0 equiv), 3 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, and 10 mol% ligand in 2.0 mL mesitylene, 60 °C under Ar for 90 h. [b]15% yield diarylation product of **8n** was isolated. [c]0.24 mmol 1,4-diiodobenzene was used, diastereomeric *dl/meso* ratio of = 88:12 determined by HPLC, 20% yield **8g** was isolated.

Enantioselective Arylation of Aryl Sulfenate Anions. Inspired by the above good result, we turned to examine whether the catalyst system is applicable to the enantioselective synthesis of diaryl sulfoxides (Scheme 7). With the *tert*-butyl 3-(phenylsulfinyl)propanoate **1w** as the starting material, various aryl iodides **2** bearing electron-donating groups, such as 4-methoxy, 4-methyl, and 4-phenyl were well tolerated and the desired diaryl sulfoxides **8a-8c** were isolated in moderate yields with 86-91% ee. The enantiomers of **8a** (**ent-8a**) and **8c** (ent-**8c**) could be also easily obtained by the simple exchang-

ing the sulfenate and halide components. Various electron-withdrawing substituents such as cyano, acetyl, formyl, esters, and halide at the *para* positions of aryl iodides reacted smoothly to give the products **8d-8l** in 45-85% yields and 89-93% ee. Notably, halogens groups provide the handle for further functionalization. Reaction between 1,4-diiodobenzene and excess sulfenate precursor gave the product of **8n** in 46% yield with 98% ee and 88:12 (*dl*/*meso*) ratio. Gratifyingly, heteroaryl iodides such as 6-iodoquinoline was well compatible to nicely afford the desired products **8o** (82% yield, 93% ee).

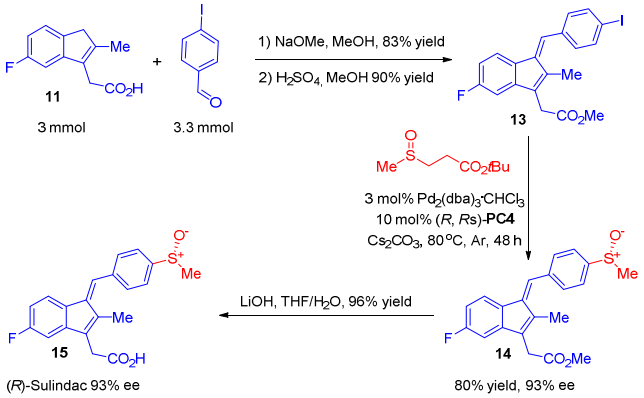
Scheme 8. Gram-scale synthesis of **3a** and synthetic transformations.



Gram-scale Synthesis and Synthetic Applications. The practicability of our method was demonstrated with a 7 mmol scale of reaction, delivering 1.15 g of **3a** in 76% yield without loss of the enantioselectivity (Scheme 8a). A Pd-catalyzed olefination through Csp^2–H activation worked smoothly,[13a] furnishing the C-H functionalization product **9** in 60% isolated yield with 90% ee. Sulfoximines are emerging as valuable motif for drug discovery, sulfoximine **10** could be efficiently prepared in 83% yield with 95% ee following the simple procedure developed by Luisi and Bull (Scheme 8b).[13b]

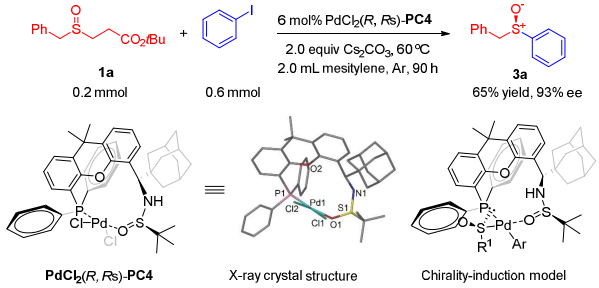
Sulindac is a nonsteroidal anti-inflammatory drug (NSAID) of the arylalkanoic acid class that is marketed in the UK & U.S. by Merck, which has shown additional utility in cancer treatment.[14] Gratifyingly, a new synthetic route for the chiral Sulindac was developed by us from the commercially available **11**(Scheme 9). The condensation with the 4-iodobenzaldehye and esterification, followed by the asymmetric cross-coupling reaction efficiently delivered the key ester intermediate **14** in high yield and 93% ee. After further hydrolysis, (*R*)-sulindac was obtained in 96% yield without loss of the enantioselectivity.

Scheme 9. Enantioselective synthesis of sulindac.



Palladium (II) Complex Catalytic Activity Study. The absolute configuration of **PC4** and the binding mode of its palladium complex were established by X-ray crystallography. The crystal structure of **PC4**/$PdCl_2$ showed that the palladium atom was clamped into an eleven-membered ring via the P and O coordination, that is, **PC4** is a new type of O, P-chiral ligand. Furthermore, subjection of this **PC4**/$PdCl_2$ complex to the reaction conditions delivered **3a** in 65% yield with 93% ee (Scheme 10), indicating that this eleven-membered palladium(II) complex has the similar catalytic activity with those palladium(0) complex *in-situ* generated from the $Pd_2(dba)_3{\cdot}CHCl_3$ with the ligand. In light of the absolute configuration of structures palladium(II) complex and the absolute configuration of product **3a**, a chirality induction model for stereochemical induction proposed. According to the previous works on the Pd/Xantphos-catalyzed cross-coupling reactions,[15] we proposed that the initial oxidative addition of palladium to aryl halides would give a Pd(II) complex, in which the aryl group is *trans* to halide. After the isomerization of the intermediate from *trans*- to the high reactive *cis*-form,[15a,c] the reductive elimination would take place rapidly to give the optically active sulfoxides (*R*)-**3a**.

Scheme 10. Palladium (II) complex catalytic activity study.



CONCLUSION

In summary, we have developed a robust catalyst system Pd/PC-Phos for the asymmetric arylation of aryl, benzyl and alkyl sulfenate anions to various chiral sulfoxides in good yields (up to 98%) with excellent enantioselectivities (up to 99% ee). It is noteworthy the chiral sulfinamide monophosphine and palladium can form a rarely observed 11-membered ring via coordination of the phosphine and the O-atom of the sulfonamide moiety. Moreover, optically active sulfoxides could potentially be used as chiral ligand and bioactive molecules. The salient features of this transformation including mild reaction conditions, general substrate scope, well functional group tolerance, good yields and high enantioselectivity, readily available starting materials, easy scale-up and application in late stage modification of bioactive compounds make this method extremely attractive. Further explorations of this new chiral ligands in arylation alkyl sulfenate anions with aryl (pseudo)halides[16] and other transition-metal asymmetric catalysis are currently underway in our group.

ASSOCIATED CONTENT

Supporting Information

Experimental procedure, optimization tables, characterization data for all the products (PDF).

AUTHOR INFORMATION

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Author Contributions

Notes

The authors declare no competing financial interests.

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(16) when **1r** and 4-chlorophenyl trifluoromethanesulfonate as the model substrates, Replaced Cs_2CO_3 with K_3PO_4 in toluene, the product was afforded in low yield (15%) with 92% ee.

(17) (CCDC) 1559331 (**3a**), 1559332 (**8k**), 1559333 ((*R*, *R*s)-**PC**4), 1559334((*R*, *R*s)-**PC4**/$PdCl_2$).

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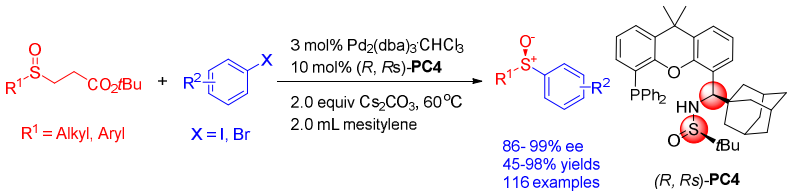

√ ***General substrate scope: aryl ary sulfoxide, aryl benzyl sulfoxide, aryl alkyl sulfoxide***

√ ***a rare eleven-membered palladium(II) complex*** √ **gram-scale synthesis and late-stage modification**