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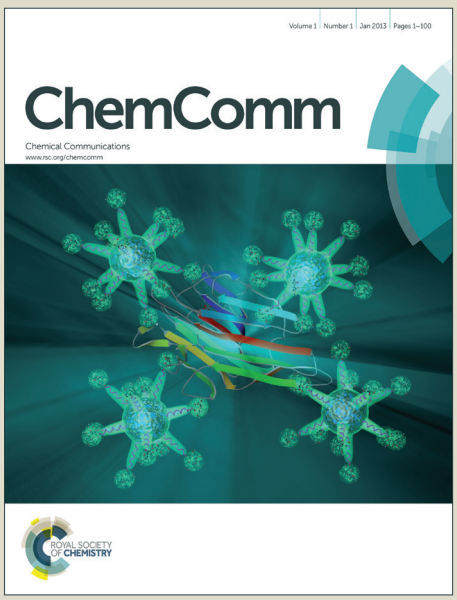

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ARTICLE TYPE

Rational design of sulfoxide-phosphine ligands for Pd-catalyzed enantioselective allylic alkylation reactions

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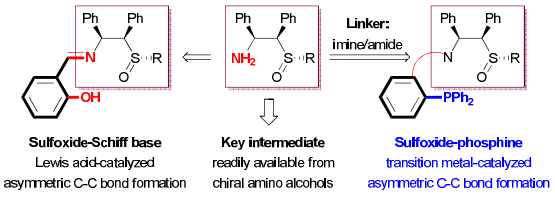
A new type of chiral sulfoxide–phosphine ligands have been developed by rational combination of two privileged scaffolds for Pd-catalyzed asymmetric allylic alkylation reactions. Under optimized conditions, generally high yields (up to 97%) and excellent enantioselectivities (up to >99% ee) were obtained.

The increasing demand for enantiopure compounds for pharmaceuticals, agrochemicals, and materials has catapulted asymmetric catalysis to be one of the most important frontiers in chemical sciences.[1] Not surprisingly, the search for high synthetic efficiency and enantioselectivity continues to stimulate the development of innovative strategies and concepts for catalyst and ligand design. New chiral catalysts and ligands are usually prepared from natural chiral sources or through the modification of existing chiral scaffolds. In this regard, the latter provides a promising platform for design of new efficient ligands since a wealth of powerful ligands have been identified and employed in asymmetric transition-metal catalysis over past several decades.[2] Recently, a new strategy involving *rational combination of two privileged backbones into one molecule* was adopted in our laboratory for the design of novel organocatalysts.[3] Along this line, we recently developed a new type of sulfoxide-Schiff base ligands, which exhibited excellent efficiency and stereoselectivities in the Cu-catalyzed asymmetric Henry reaction (Scheme 1).[4] More importantly, the chiral sulfoxide-amino unit has proved to be critical to the stereoinduction. Encouraged by these results, we attempted to design other new sulfoxide-containing ligands by merging such sulfoxide-amino units with aryl phosphine units for transition-metal catalyzed asymmetric carbon-carbon bond formation processes (Scheme 1).

Palladium-catalyzed asymmetric allylic alkylation (AAA, also named as Tsuji-Trost reaction) represents one of the most powerful synthetic methods for the construction of various carbon-carbon and carbon-heteroatom bonds.[5] As a result, numerous efficient chiral ligands have been developed for this transformation. However, the use of *S*-chiral sulfoxide ligands has not yet been extensively explored for this reaction.[6] Since the pioneering work by Shibasaki,[7] a wide range of chiral sulfoxide ligands have thereafter been designed for Tsuji-Trost reactions, such as bis-sulfoxide,[8] sulfoxide-phosphine,[9] sulfoxide-oxazoline,[10] sulfoxide-amine[11] and sulfoxide-sulfide.[12] In spite of these impressive contributions, the development of more efficient sulfoxide-based ligands for the Pd-catalyzed AAA reactions remains highly desirable. Herein, we wish to communicate the development of a new type of sulfoxide-phosphine ligands by combining sulfoxide-amino with a soft base element, aryl phosphine unit, and their application in the Pd-catalyzed AAA reactions.



Scheme 1 Design of chiral sulfoxide-phosphine ligands.

Initially, sulfoxide ligand **2** containing imino-phosphine motif was successfully synthesized by the condensation of 2-(diphenylphosphino)benzaldehyde with our key intermediate chiral sulfoxide amine[4] (see ESI for details). Compared with the previous chiral sulfoxide-Schiff base **1** (48 h, trace), greatly improved reaction efficiency was observed in the model reaction of *rac*-(*E*)-1,3-diphenylallyl acetate **4a** and dimethyl malonate **5a** (95% yield) (Scheme 2). Unfortunately, poor enantioselectivity was obtained (37% *ee*). We expected that, replacing the basic imine linker between the sulfoxide-amino and phosphine units with an amide group would result in good enantioselectivity preserving the high yield. Similarly, the target ligand **3a** can be easily prepared with a high yield from commercially available 2-(diphenylphosphino)benzoic acid and our key intermediate, enantiopure sulfoxide amine (see ESI for details). To our delight, the use of ligand **3a** resulted in the formation of the corresponding product with 97% *ee*, albeit in moderate yield (46%), which suggested that the absolute configurations of diamine and sulfoxide moieties in **3a** matched well with each other (Scheme 2). Replacement of the imine linker in **2** with amide group was beneficial for the coordination of Pd species with both phosphine and sulfoxide groups, and therefore provided a better steric environment for asymmetric induction.[6] To evaluate the effects of the sulfoxide group and phosphine moiety

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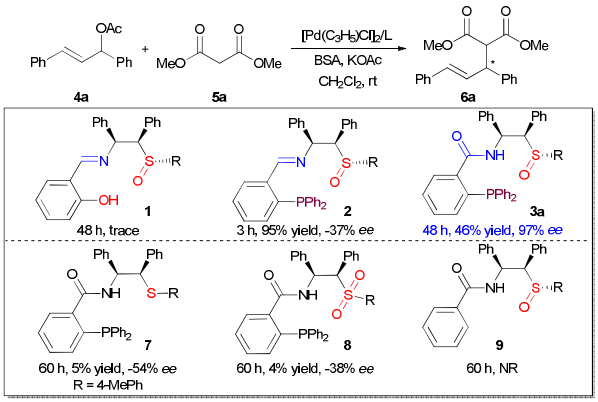
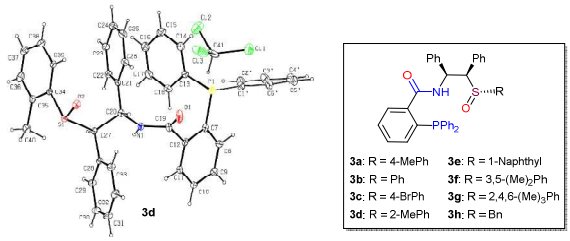
on the catalytic performance, we have designed analogous ligands **7-9** for control experiments. The poor results with ligands **7-9** revealed that both chiral sulfoxide group and phosphine moiety were essential for the high efficiency and enantioselectivity of the model reaction.



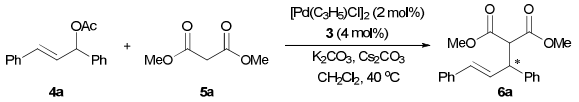
Scheme 2 Initial attempts and control experiments.



Scheme 3 Chiral sulfoxide-phosphines and X-ray structure of **3d**.

To further improve the chemical yield and enantioselectivity, we continued to optimize reaction conditions. Screening of various bases[13] and temperature indicated that a mixture of K_2CO_3 and Cs_2CO_3 at 40 °C gave optimal results (Table 1S in ESI). In addition, investigation of catalyst loading showed that 2 mol% of $[Pd(C_3H_5)Cl]_2$ was enough for reaching high reaction efficiency and stereoselectivity (Table 4S in ESI). Encouraged by these preliminary results, we have synthesized a small library of chiral sulfoxide-phosphine ligands with different substituents on sulfoxide moiety (Scheme 3) and examined their catalytic efficiency in the model AAA reaction. As highlighted in Table 1, most of the sulfoxide-phosphine ligands proved to be effective for the model reaction, giving **6a** in good yields with high enantioselectivities (97-99% yields, 84.0-99.0% ee). It was found that the electronic properties of the sulfoxide group had little influence on this reaction (Table 1, entries 1-6). In the case of ligand **3g**, the reaction became sluggish and the enantiomeric excess dramatically decreased to 87.0% (Table 1, entry 7), suggesting that a sterically bulky R group would disfavour the coordination and stereoinduction. Moreover, incorporation of the aliphatic group into the ligand, such as **3h**, also resulted in an obvious decrease in catalytic efficiency and enantioselectivity (Table 1, entry 8, 84.0% ee).

Table 1 Ligand screening[a]

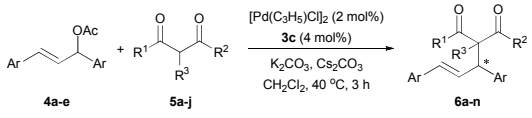


Entry	Ligand	Time (h)	Yield[b] (%)	Ee[c] (%)
1	**3a**	3	99	98.8
2	**3b**	3	99	98.8
3	**3c**	**3**	**99**	**99.0**
4	**3d**	3	99	98.6
5	**3e**	3	99	98.7
6	**3f**	3	99	98.4
7	**3g**	12	98	87.0
8	**3h**	12	97	84.0

[a] Unless otherwise noted, reactions were carried out with **4a** (0.3 mmol), **5a** (0.9 mmol), $[Pd(C_3H_5)Cl]_2$ (2 mol%), **3** (4 mol%), K_2CO_3 (0.75 mmol) and Cs_2CO_3 (0.15 mmol) in CH_2Cl_2 (3.0 mL) at 40 °C. [b] GC yield. [c] Determined by chiral HPLC, the absolute configuration was established as *S* by comparison with literature data.

With optimal chiral sulfoxide-phosphine ligand **3c** in hand, we then investigated the substrate scope of this Pd-catalyzed AAA reactions under optimized reaction conditions. As shown in Table 2, a variety of symmetric 1,3-dicarbonyl compounds **5a-5g** can react with *rac*-(*E*)-1,3-diphenylallyl acetate **4a** efficiently to afford the corresponding products **6a-6g** with excellent yields and enantioselectivities (Table 2, entries 1-7, 93-97% yields, 97.4-99.3% ee). The unsymmetric 1,3-dicarbonyl compounds, such as **5h-5j**, can also participate in this transformation; however, diastereoselectivities are not good (Table 2, entries 8-10). Notably, this reaction exhibited high tolerance of the 1,3-diphenylallyl acetate components. For example, substrates bearing either the electron-donating or electron-withdrawing substituents on the aromatic ring underwent the reaction smoothly to give the desired products in good yields with high levels of enantioselectivities (Table 2, entries 11-14, 86-95% yields, 98.0-98.5% ee).

Table 2 Substrate scope[a]



4a: Ar = Ph
4b: Ar = 4-MePh
4c: Ar = 4-FPh
4d: Ar = 4-ClPh
4e: Ar = 4-BrPh

5a: $CH_2(CO_2Me)_2$
5b: $CH_2(CO_2Et)_2$
5c: $CH_2(CO_2{}^iPr)_2$
5d: $CH_2(COMe)_2$
5e: $CH_3CH(CO_2Et)_2$
5f: $PhCH(CO_2Et)_2$
5g: $C_3H_5CH(CO_2Et)_2$
5h: $CH_3COCH_2CO_2Et$
5i: $PhCOCH_2CO_2Et$
5j: $CH_3COCH(CH_3)CO_2Et$

Entry	4	5	Product	Yield[b] (%)	Ee[c] (%)
1	**4a**	**5a**	**6a**	96	99.0 (*S*)
2	**4a**	**5b**	**6b**	95	99.0 (*S*)
3	**4a**	**5c**	**6c**	94	98.8 (*S*)
4	**4a**	**5d**	**6d**	97	97.4 (*S*)
5	**4a**	**5e**	**6e**	95	99.1 (*R*)
6	**4a**	**5f**	**6f**	93	98.7 (*R*)
7	**4a**	**5g**	**6g**	93	99.3 (*R*)
8	**4a**	**5h**	**6h**	96	98.6/98.4[d]
9	**4a**	**5i**	**6i**	94	98.5/98.3[e]
10	**4a**	**5j**	**6j**	93	98.6/96.0[f]
11	**4b**	**5a**	**6k**	86	98.2 (*S*)
12	**4c**	**5a**	**6l**	93	98.5 (*S*)
13	**4d**	**5a**	**6m**	92	98.0 (*S*)

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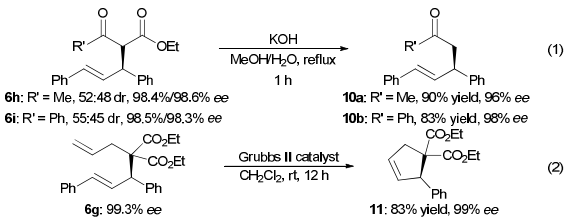
14	**4e**	**5a**	**6n**	95	98.3 (*S*)

[a] Unless otherwise noted, reactions were carried out with **4** (0.3 mmol), **5** (0.9 mmol), $[Pd(C_3H_5)Cl]_2$ (2 mol%), **3c** (4 mol%), K_2CO_3 (0.75 mmol) and Cs_2CO_3 (0.15 mmol) in CH_2Cl_2 (3.0 mL) at 40 °C for 3 h. [b] Isolated yield. [c] Determined by chiral HPLC, the absolute configuration was established by comparison with literature data. [d] The d.r. was 52:48 as determined by chiral HPLC and ^{1}H NMR. [e] The d.r. was 55:45 as determined by chiral HPLC and ^{1}H NMR. [f] The d.r. was 55:45 as determined by chiral HPLC and ^{1}H NMR.

To demonstrate the synthetic potential of the AAA products, we removed the ester group of products **6h** and **6i** under the basic condition in refluxing $MeOH/H_2O$.[14] After 1 h, the corresponding products **10a** and **10b** can be obtained in high yields without any loss of enantiomeric excess (eq 1). More importantly, product **6g** has been successfully applied in a convenient synthesis of the cyclopentene **11** by ring-closing metathesis (eq 2).[15]



In summary, we have developed a new class of chiral sulfoxide-phosphine ligands by rational combination of chiral sulfoxide-amino scaffold and soft basic phosphine group. These new ligands were found to be highly efficient for Pd-catalyzed AAA reactions, affording the corresponding products with excellent yields (up to 97%) and enantioselectivities (up to >99% ee). Studies on possible coordination mode between metal and ligand, and further applications of this type of ligands to other transformations are currently ongoing in our laboratory.[16]

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† Electronic Supplementary Information (ESI) available: Experimental procedures and compound characterisation data, including X-ray crystal data for **3d** (CCDC971186). For ESI and crystallographic data in CIF or other electronic format See DOI: 10.1039/b000000x/

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