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Highly Enantioselective Pd-Catalyzed Allylic Alkylation of Indoles Using Sulfur-MOP Ligand

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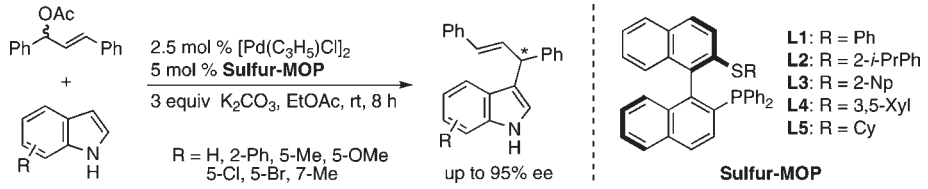
ABSTRACT



The preparation of various (*R*)-Sulfur-MOP ligands with aryl and alkyl substituents on sulfur, and the application of these ligands to Pd-catalyzed asymmetric allylic alkylation of indoles is reported. The sulfur substituent served as an effective stereocontrol element, and in the case of the 2-*i*-PrPh substituent on sulfur, the allylation products from an array of simple and substituted indoles were obtained with high enantioselectivity (up to 95% ee).

Chiral bidentate ligands containing strong and weak donor heteroatom pairs have emerged as an important class of chiral ligands for transition metal-catalyzed enantioselective processes, because the different intensity of the trans effects of the two heteroatoms on metal-bound substrates is a powerful control element in the stereochemistry-determining step of the catalytic cycle. Among such ligands, thioether-containing phosphine ligands (P,S-ligands) have recently attracted much attention because, adjacent to the metal-bound substrate, extra chirality on sulfur is generated by coordination to the metal (sulfur chirality), thus providing an additional stereocontrol element.[1] We have previously reported the synthesis of Sulfur-MOP (**L1**), a P,S-ligand that is an analogue of BINAP. Ligand **L1** is the first MOP-type ligand containing an aryl thioether group, rather than an alkyl one.[2,3] In this letter, we report the Pd-catalyzed asymmetric allylic alkylation of indoles with aryl thioether-containing Sulfur-MOP ligands **L1**−**L4** and their alkyl counterpart **L5**. Because optically active indoles and their derivatives are

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(1) For some recent examples of chiral mixed phosphorus/sulfur ligands, see: (a) Oura, I.; Shimizu, K.; Ogata, K.; Fukuzawa, S.-i. *Org. Lett.* **2010**, *12*, 1752. (b) Hernánadez-Toribio, J.; Arrayás, R. G.; Martín-Matute, B.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 393. (c) Hernánadez-Toribio, J.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 16150. (d) López-Pérez, A.; Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 10084. (e) González, A. S.; Arrayás, R. G.; Rivero, M. R.; Carretero, J. C. *Org. Lett.* **2008**, *10*, 4335. (f) Lam, F. L.; Au-Yeung, T. T.-L.; Kwong, F. Y.; Zhou, Z.; Wong, K. Y.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 1280. (g) Cheung, H. Y.; Yu, W.-Y.; Lam, F. L.; Au-Yeung, T. T.-L.; Zhou, Z.; Chan, T. H.; Chan, A. S. C. *Org. Lett.* **2007**, *9*, 4295.

(2) Hoshi, T.; Hayakawa, T.; Suzuki, T.; Hagiwara, H. *J. Org. Chem.* **2005**, *70*, 9085.

(3) Sulfur-MOP ligands containing alkyl sulfur substituents, see: (a) Zhang, W.; Shi, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3467. (b) Gladiali, S.; Medici, S.; Pirri, G.; Pulacchini, S.; Fabbri, D. *Can. J. Chem.* **2001**, *79*, 670. (c) Gladiali, S.; Dore, A.; Fabbri, D. *Tetrahedron: Asymmetry* **1994**, *5*, 1143.

(4) For some recent reviews of biologically active indoles and derivatives, see: (a) Kochanowska-Karamyan, A.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489. (b) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532. (c) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73.

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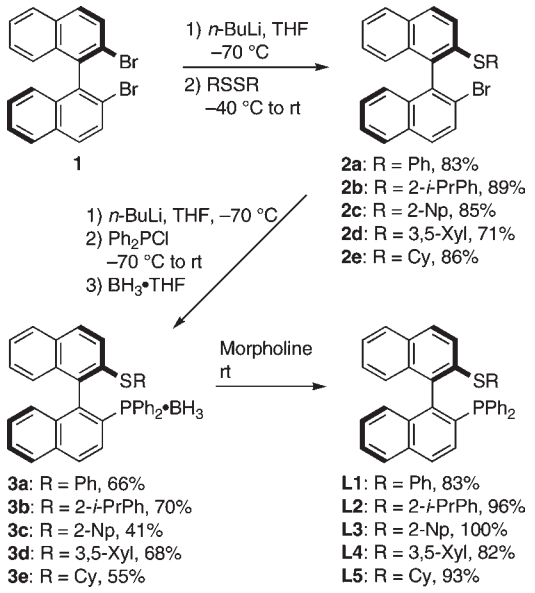
Scheme 1. Stereoretentive Preparation of Sulfur-MOP Ligand



common in biologically active natural products and pharmaceuticals,[4] chiral catalysts for the synthesis of these compounds are of great importance.[5] Recently, remarkable progress has been made in the development of catalytic asymmetric. Friedel–Crafts alkylation of indole, benefiting from its nucleophilicity.[6] In contrast, indole nucleophiles are rarely used in metal-catalyzed asymmetric allylic alkylations.[1g,7] In light of the excellent versatility of Pd-catalyzed allylic alkylation as an enantioselective C–C bond-forming process,[8] we focused on this reaction for the synthesis of optically active indoles using Sulfur-MOP ligands. As expected, the steric and electronic properties of sulfur chirality had a strong effect on enantioselectivity; the ligand **L2**, which contains a 2-*i*-PrPh group as the sulfur substituent, was found to be the best Sulfur-MOP ligand, providing the allylation products in high enantioselectivity (up to 95% ee). Also, to ensure the availability of the required sulfur substituents, we developed a more robust synthetic route to the Sulfur-MOP ligands, because our previous route included a step in which axial chirality was lost due to racemization.[2]

(5) For a review, see:Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608.

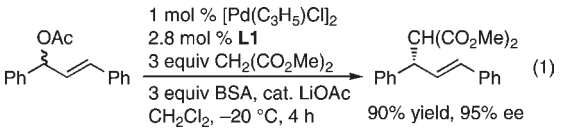
(6) For recent reviews of catalytic asymmetric Friedel–Crafts alkylations of indoles, see: (a) Zeng, M.; You, S.-L. *Synlett* **2010**, 1289. (b) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, 2190. (c) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (d) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550.

(7) (a) Wu, Q.-F.; He, H.; Liu, W.-B.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 11418. (b) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9553. (c) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L *Synthesis* **2009**, 2076. (d) Onitsuka, K.; Kameyama, C.; Sasai, H. *Chem. Lett.* **2009**, *38*, 444. (e) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2008**, *10*, 1815. (f) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (g) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424.

(8) For some reviews, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Helmchen, G. *J. Organomet. Chem.* **1999**, *567*, 203. (c) Trost, B. M.; Vranken, D. L. V. *Chem. Rev.* **1996**, *96*, 395.

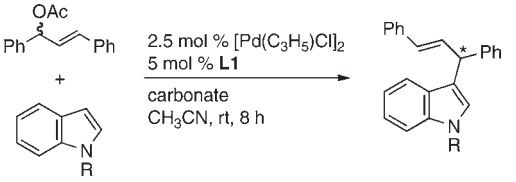
Sulfur-MOP ligands **L1**–**L5** could be prepared in enantiomerically pure form via the sulfenylation of (*R*)-dibromobinaphthyl (**1**),[9] followed by the phosphination of the resulting bromosulfide (**2**) (Scheme 1). Here, the order of the substitution sequence is opposite that of our previous route because the phosphination product of **1** is easily racemized during lithiation in the subsequent sulfenylation step.[2,10] As expected, the reversed substitution sequence allowed the axial chirality to be completely retained over the course of the entire ligand synthesis without any special precautions in the experimental procedure. To prevent the oxidation of the phosphine during workup, the substitution product was isolated as the BH_3-protected phosphine **3**. Deprotection using morpholine as the BH_3 scavenger provided the corresponding Sulfur-MOP ligand in almost quantitative yield.

In the initial study, we examined the catalyst generated from $[Pd(C_3H_5)Cl]_2$ and Sulfur-MOP ligand **L1**, which contains a Ph group as the sulfur substituent, in the reaction of dimethyl malonate with 1,3-diphenylpropenyl acetate (eq 1). After the conditions were optimized, the product was obtained in 90% yield and 95% ee.



This high catalytic performance encouraged us to examine the Pd-catalyzed allylic alkylation of indoles using Sulfur-MOP ligands (Table 1). Because Chan and coworkers obtained the best result when the reaction was conducted at 40 °C in CH_3CN with two equivalents of K_2CO_3 as base,[1g] we began to examine catalysis based on **L1** under the same conditions. We found that the reaction occurred smoothly, even at room temperature, to give the allylation product in 56% yield and 82% ee in 8 h (entry 1). Fortunately, the undesired *N*-allylation did not occur.[11]

Table 1. Pd-Catalyzed Asymmetric Allylic Alkylation of Indole Using Sulfur-MOP Ligand **L1**

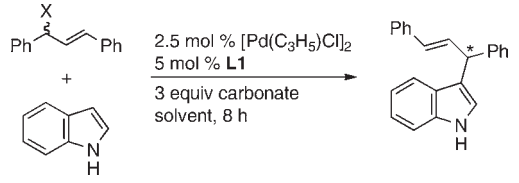


entry	R	carbonate	yield (%)[a]	% ee[b]
1	H	K_2CO_3, 2 equiv	56	82
2	H	K_2CO_3, 3 equiv	77	86
3	H	K_2CO_3, 5 equiv	69	82
4	H	K_3PO_4, 3 equiv	44	80
5	H	–	14	17
6	Me	K_2CO_3, 3 equiv	0	–

[a] Isolated yield. [b] Determined by chiral HPLC analysis.

Increasing the amount of K_2CO_3 from 2 equiv to 3 equiv favorably affected the yield, likely because of the more effective deprotonation of indole to generate the amide anion nucleophile (entry 2). However, the further addition of K_2CO_3 resulted in decreased yield (entry 3). The use of the stronger base K_3PO_4 was also ineffective at promoting the reaction (entry 4). It is noteworthy that not only the yield (14%) but also the enantioselectivity (17% ee) was reduced when the reaction was carried out without base (entry 5). The marked decrease in enantioselectivity in this case indicates that the base plays an important role, not only promoting the reaction but also inducing the enantioselectivity. The lack of reactivity of *N*-methylindole is consistent with our speculation that the amide anion, rather than indole, is the effective nucleophile that attacks the palladium π-allyl intermediate in the catalytic cycle (entry 6).

Table 2. Optimization of Reaction Conditions



entry	X	carbonate	solvent	temp (°C)	yield[a] (%)	% ee[b]
1	OAc	K_2CO_3	EtOAc	rt	86	83
2	OAc	K_2CO_3	THF	rt	89	81
3	OAc	K_2CO_3	DME	rt	74	81
4	OAc	K_2CO_3	toluene	rt	83	81
5	OAc	K_2CO_3	CH_2Cl_2	rt	86	69
6	OAc	K_2CO_3	CH_3CN	rt	77	86
7	OAc	Li_2CO_3	EtOAc	rt	0	–
8	OAc	Na_2CO_3	EtOAc	rt	41	71
9	OAc	Cs_2CO_3	EtOAc	rt	62	82
10	OAc	$CaCO_3$	EtOAc	rt	0	–
11	OAc	$SrCO_3$	EtOAc	rt	32	23
12	OAc	$Y_2(CO_3)_2$	EtOAc	rt	0	–
13	OAc	$Ce_2(CO_3)_2$	EtOAc	rt	0	–
14	OAc	K_2CO_3	EtOAc	0	57	84
15	OAc	K_2CO_3	EtOAc	40	57	71
16	OCO_2CH_3	K_2CO_3	EtOAc	rt	87	71
17	OCO_2CH_3	–	EtOAc	rt	69	8

[a] Isolated yield. [b] Determined by chiral HPLC analysis.

Having verified the efficiency of the catalytic system based on Sulfur-MOP ligand **L1**, we pursued further optimization of the reaction conditions (Table 2). The catalyst worked well in various polar and nonpolar solvents (entries 1−6). Among them, EtOAc was the second best solvent in terms of both yield and enantioselectivity. Because of the practical advantages of EtOAc, namely, safety and low cost, it was selected as the solvent for the optimized catalytic system. In contrast to the high solvent tolerance, the catalytic performance was highly dependent on the identity of the base (entries 7−13).[12] Because potassium carbonate was found to give better results than potassium phosphate in the initial study, we surveyed carbonates of alkali metals, alkaline earth metals, yttrium, and cerium in an attempt to optimize the base further. Unfortunately, none of these metal carbonates further enhanced the activity and selectivity of the catalyst; accordingly, K_2CO_3 was used as the base for the optimized catalytic system. The catalyst exhibited the best performance at room temperature. The reaction at 0 °C resulted in considerably lower yield, while the enantioselectivity remained invariant (entry 14). Conducting the reaction at 40 °C resulted in both lower yield and lower enantioselectivity (entry 15). The replacement of allyl acetate by allyl carbonate led to lower enantioselectivity due mainly to the influence of in situ-generated methoxide base on the stereochemistry-determining step (entry 16). In fact, in contrast to allyl acetate, the reaction with allyl carbonate smoothly proceeded even in the absence of basic additive, but gave the almost racemic product (entry 17). Consequently, we selected allyl acetate, EtOAc, K_2CO_3, and room temperature as the allylation reagent, the solvent, the base, and the reaction temperature.

Having found the optimized conditions, we next examined Sulfur-MOP ligands containing 2-*i*-PrPh, 2-naphthyl (2-Np), 3,5-xylyl (3,5-Xyl), and cyclohexyl (Cy) groups as sulfur substituents to evaluate the importance of sulfur chirality as a stereocontrol element of the ligand architecture. We also expected that tuning sulfur chirality by changing the sulfur substituent would produce further enhancement in the catalyst's enantioselectivity. As shown in Table 3, all three aryl substituents on sulfur served as effective stereocontrol elements, as did the Ph sulfur substituent (entries 1−3). Among them, 2-*i*-PrPh induced the highest enantioselectivity, providing the allylation product in 92% ee and 83% yield (entry 1). The replacement of the aryl substituents on sulfur by their alkyl counterpart, Cy, more clearly exhibited the influence of the sulfur chirality on the enantioselectivity of the catalyst, which was dramatically changed to give the opposite absolute configuration of the product (entry 4). To gain additional insight into the effects of sulfur chirality, we also examined (*R*)-MeO-MOP[13] and (*R*)-BINAP,[14] the binaphthyl-based P,X-ligands containing oxygen and phosphorus instead of sulfur as the heteroatom X, respectively. The catalyst based on (*R*)-MeO-MOP exhibited comparable enantioselectivity, but moderate yield (entry 5). The use of (*R*)-BINAP, which can be regarded as the complete phosphorus counterpart of Sulfur-MOP ligand **L1**, led to a significant loss in the

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(10) Shimada, T.; Kurushima, H.; Cho, Y.-H.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 8854.

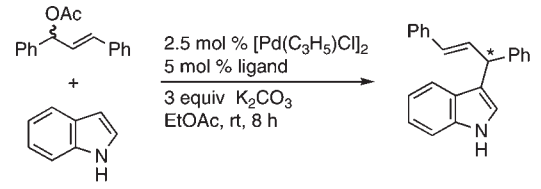
(11) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* **2004**, *6*, 3199.

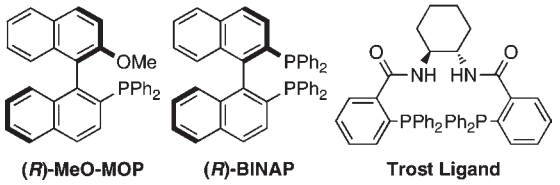
(12) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089. Chan and co-workers also reported the significant effect of base on the enantioselectivity of Pd-catalyzed asymmetric allylic alkylations of indole. See ref 1g.

(13) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354.

(14) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

Table 3. Ligand Effect





entry	ligand	yield (%)[a]	% ee[b]
1	**L2**	83	92
2	**L3**	58	82
3	**L4**	89	78
4	**L5**	68	−48
5	(*R*)-MeO-MOP	45	−85
6	(*R*)-BINAP	32	44
7	Trost ligand	6	<1

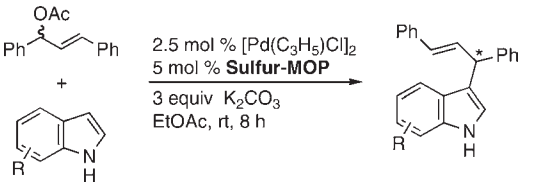
[a] Isolated yield. [b] Determined by chiral HPLC analysis.

activity and selectivity (entry 6). The Trost ligand,[15] which has also found widespread use as a chiral C_2-symmetric P, P-ligand, gave only the racemic product in low yield (entry 7). Although the mechanism of the enhancement of the catalytic activity and selectivity remains unknown, the difficulty in achieving high catalytic performance even through the use of these outstanding chiral ligands also exhibits the exceptional efficiency of Sulfur-MOP ligand **L2** in this asymmetric reaction.

The catalyst based on ligand **L2** also worked well in the reactions of substituted indoles to afford the corresponding products in up to 95% ee (Table 4, entries 1−6). The enantioselectivity was highly dependent on the electronic properties of the substituents at the 5- and 7-positions: the enantioselectivity for electron-donating groups was higher than that for electron-withdrawing groups (entries 1−5). Because of unfavorable steric interactions, a bulky substituent on the pyrrole ring led to deterioration in both the yield and enantioselectivity (entry 6). The use of ligand **L2** in the reactions of these substituted indoles resulted in ee values 10−25% higher than those in the case of the parent ligand **L1** (entries 1−6 vs entries 7−12). A similar degree of

(15) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.

Table 4. Scope of Indoles



entry	R	**Sulfur-MOP**	yield (%)[a]	% ee[b]
1	5-Br	**L2**	67	78
2	5-Cl	**L2**	88	83
3	5-Me	**L2**	85	95
4	5-MeO	**L2**	84	93
5	7-Me	**L2**	76	90
6	2-Ph	**L2**	66	66
7	5-Br	**L1**	80	68
8	5-Cl	**L1**	76	58
9	5-Me	**L1**	75	83
10	5-MeO	**L1**	87	81
11	7-Me	**L1**	60	79
12	2-Ph	**L1**	54	52

[a] Isolated yield. [b] Determined by chiral HPLC analysis.

improvement was seen for the reaction of the simple indole. These results demonstrate the importance of sulfur chirality as the stereocontrol element in our catalytic system.

In summary, we have developed a method for highly enantioselective Pd-catalyzed allylic alkylation of indoles, using Sulfur-MOP ligands. Tuning of the sulfur chirality by changing the structural properties of the sulfur substituent was an effective stereocontrol tactic. The allylation products derived from an array of the simple and substituted indoles could be obtained with high enantioselectivity (up to 95% ee) in the case of ligand **L2**. The catalytic performance was also strongly dependent on the identity and amount of added base. In contrast, the catalyst system exhibited broad solvent tolerance. To prepare ligands with a structurally diverse array of sulfur substituents, we also developed a racemization-free route to Sulfur-MOP ligands. Further exploration of the potential of Sulfur-MOP ligands is underway in our laboratory.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.