## New Chiral N, S-Ligands with Thiophenyl at Benzylic Position. Palladium (II)-catalyzed Enantioselective Allylic Alkylation

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New chiral N, S-ligands with oxazoline and thiophenyl substituents at benzene ring and benzylic position have been prepared and applied in palladium-catalyzed asymmetric allylic alkylation reaction to provide the product with high yield and entantioselectivity (82%—93% ee).

**Keywords** N, S-ligands, palladium-catalyst, asymmetric allylic alkylation

Chiral ligands play a crucial role in asymmetric catalysis. To date a variety of ligands have been synthesized and proved to be effective. Among them the ligands 1 with both coordinate atoms at benzene ring-positions show good to excellent asymmetric induction in catalytic asymmetric reactions. 1 However, little attention has been paid to ligands 2 with coordinating atoms fixing at benzylic and benzene ring positions although the structure of 2 seems rather simple.<sup>2</sup> In a program aimed at the designs and applications of chiral ligands in asymmetric synthesis, 3 it has been found that ligand 3 is more effective than ligands 4 both in catalytic efficiency and enantioselectivity in palladium catalyzed allylic substitution.3d Since thiophenyl group is at the chiral benzylic carbon atom in ligand 3, it is not clear whether its higher efficiency is caused by the different position of thiophenyl. Thus we

decided to synthesize such kind of ligands 2 to examine the influence of the change of structure from ligands 1 to ligands 2 in catalytic asymmetric reactions. In this letter, we would like to disclose the synthesis of ligands 5 and their applications in palladium catalyzed allylic substitutions.

$$X = S, Se$$

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$$X = IPr; b, R = IBu; c, R = Bn$$

Syntheses of ligands 5 were readily achieved as follows: Treatment of o-toluic acid 6 with oxalyl chloride

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followed by amino alcohols afforded chiral amides 7. Subsequent reaction of 7 with triphenylphosphine provided oxazolinyl toluene 8. Direct benzylic-lithiatiation of 8 with BuLi and an equimolar amount of TMEDA followed by quenching with PhSSPh gave rise to the expected products 5a-5c (Scheme 1). All products were purified by flash chromatography and gave satisfactory analysis results.

## Scheme 1

COOH 1) (COCl)<sub>2</sub> CH<sub>2</sub>Cl<sub>2</sub>
2) R
6 H<sub>2</sub>N OH 7

Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>
96% 
$$-98\%$$
1) BuLi (1.5 equiv.)

TMEDA (1.5 equiv.)

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2) PhSSPh
60%  $-65\%$ 

PhS

 $\mathbf{a}$ ,  $\mathbf{R} = {}^{i}\mathbf{Pr}$ ;  $\mathbf{b}$ ,  $\mathbf{R} = {}^{t}\mathbf{Bu}$ ;  $\mathbf{c}$ ,  $\mathbf{R} = \mathbf{Bn}$ 

Then asymmetric palladium catalyzed allylic substitution reaction was chosen as test reaction.<sup>4</sup> Thus treatment of 1,3-diphenylprop-2-enyl-1-acetate (9) with the anion of dimethylmalonate in the presence of catalytic amount of palladium complex and ligands 5a-5c afforded the substitution product 10 (Scheme 2).

## Scheme 2

Firstly, the effect of different salts and solvents on the yields and enantioselectivities of the reaction by using ligand **5a** and the reaction conditions which achieved excellent results in our previous work (Table 1) were investigated.  $^{3a,3d}$  It was found that all reactions gave excellent yields whether the salt was added or not, but the reaction time was longer if there was no salt (Entry 4). Also, the reaction provided the highest ee when it proceeded in  $CH_2Cl_2$  and KOAc as additive (Entry 2).

Table 1 Asymmetric palladium catalyzed allylic substitution with different salts and solvents<sup>a</sup>

Entry	Solvent	Additive	Time (h)	Yield (%)	ee (%) <sup>b</sup>
1	MeCN	KOAc	5	99	84(S)
2	$CH_2Cl_2$	KOAc	4	99	89(S)
3	$CH_2Cl_2$	LiOAc	3	98	82(S)
4	$CH_2Cl_2$	None	15	98	75(S)

<sup>a</sup> Reaction conditions: 2.5 mol% [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub>, 5 mol% ligand **5a**, 3 mol% salt, 300 mol% CH<sub>2</sub> (CO<sub>2</sub>Me)<sub>2</sub>, 300 mol% BSA. <sup>b</sup> The enantiomeric excess was determined by HPLC, and the absolute configuration of the product was determined by comparison of the optical rotation with literature values.<sup>5</sup>

In view of the reaction time, yield and ee value, the dichloromethane and the potassium acetate were used in examination of efficiency of ligands 5 and the results were showed in Table 2. Compared with the palladium complexes of chiral thioethers of phenyloxazoline ligands 11 reported by Williams, 1d the palladium complexes with chiral benzylthioethers of our's are more efficient. Under similar conditions, the enantioselectivity close to that Williams obtained (88% in Entry 1 vs. 90% in Entry 11, 93% in Entry 2 vs. 96% in Entry 10), but the reactions proceeded much faster (0.6 h in Entry 1 vs. 36 h in Entry 11, 0.75 h in Entry 2 vs. 96 h in Entry 10). When the amount of ligand was varied from 10 mol% to 5 mol%, there was little change in ee values (88% in Entry 1 vs. 89% in Entry 4, 93% in Entry 2 vs. 92% in Entry 5) as the amount of ligand down to 5 mol% with little longer reaction time. Even the amount of ligands was down to 1 mol%, high ee was also provided and ligand 5c gave almost quantitative yield and good enantioselectivity (Entry 8).

PhS O '''/R 11a, 
$$R = {}^{i}Pr$$
 11b,  $R = {}^{t}Bu$ 

	Table 2	Conversion	of 9 into	10	with	palladium	catalyst	and	enantiomerically pure ligands <sup>a</sup>	
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Entry	Ligand (L)	Catalyst (Pd) (mol%)	ligand (mol%)	Time (h)	Yield (%)	ee (%)b
1	5a	5	10	0.6	98	88(S)
2	5b	5	10	0.75	98	93(S)
3	5c	5	10	0.5	99	83(S)
4	5a	2.5	5	3.5	98	89(S)
5	5b	2.5	5	4	99	92(S)
6	5c	2.5	5	2	99	84(S)
7	5a	0.5	1	120	60	82(S)
8	5b	0.5	1	120	55	90(S)
9	5c	0.5	1	68	98	84(S)
10	$11b^a$	5	10	96	92	96(S)
11	11a <sup>a</sup>	5	10	36	96	90(S)

<sup>&</sup>lt;sup>a</sup>Reaction conditions: the amount of  $[Pd(\eta^3-C_3H_5)Cl]_2$  and ligands as indicated, 3 mol% salt, 300 mol%  $CH_2(CO_2Me)_2$ , 300 mol% BSA, 20 °C. <sup>b</sup> The enantiomeric excess was determined by HPLC, and the absolute configuration of the product was determined by comparison of the optical rotation with literature values.<sup>5</sup>

These results and our previous studies<sup>3e</sup> clearly show that the ligands with the two coordinating atoms at benzylic and benzene ring-positions are more effective thanthat with both the coordinating atoms at benzene ring-positions in catalytic efficiency. This is presumably due to the increased tether length between the donor atoms that coordinate closer to the allyl species during the reaction.<sup>6</sup>

In summary, several novel oxazolinyl toluene ligands containing thiophenyl at benzylic position, which are more effective than that with two substituents at benzene ring, have been prepared. Further studies regarding the synthesis of ligands 2 with other kind of coordination atoms and their applications in asymmetric catalysis, the reason why the ligands 5 give high catalytic efficiency are under further investigation.

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