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Preparation of S-Containing Aminophosphine and Phosphoramidite Ligands and Their Applications in Enantioselective C–C Bond Forming Reactions

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Abstract A series of phosphorus/sulfur ligands were readily prepared and successfully applied in the Pd-catalyzed enantioselective allylic substitution and Cu-catalyzed conjugated additions of cyclic enones, respectively. The Pd-catalyzed enantioselective allylic substitution showed the best yield of 98% with 74% ee. For the Cu-catalyzed conjugated additions of cyclic enones, the best yield of 100% with 76% ee at the temperature of −30 °C could be obtained.

Keywords Phosphorus/sulfur ligands · C–C bond formation · Enantioselectivity

1 Introduction

By virtue of the high coordination ability of the sulfur atom to most transition metals, asymmetric sulfur ligands have received great attention in the last 20 years [1–4]. A lot of studies revealed that sulfur-containing chiral ligands were effective in most organic reactions, such as hydrogenation [5], hydrogen transfer [6], allylic substitution [7], conjugated additions [8], Diels–Alder reactions [9] and CO-phosphine exchange reactions [10]. In recent years, significant progresses have been made in heterodonor ligands, which contain sulfur atom and strong donor heteroatom, giving rise to different electronic properties. Among the heterodonor ligands, those who containing mixed phosphorus/sulfur coordination atoms have been numerously explored, and most of these ligands were used in catalytic enantioselective C–C bond formation. In 1999, Evans et al. developed a family of thioether-phosphinite ligands which were proved to be effective in Pd-catalyzed allylic substitution reactions [11, 12]. Hiroi et al. studied the synthesis of (*s*)-proline-derived phosphines bearing various organosulfur groups for allylic substitution reactions [13–16]. Enders et al. [17, 18], Dai et al. [19], Carretero et al. [20, 21], Manoury et al. [22] and Toru et al. [23] have applied ferrocene as scaffold and synthesized a series of P/S ligands. These P/S ligands were successfully applied in Pd-catalyzed enantioselective C–C bond forming reactions. In addition, axially chiral P/S heterdonor ligands, BINAPS, bearing excellent catalytic effects were reported by She [24], Gladiali [25] and Shi [26].

Recently, a series of chiral phosphorus ligands derived from α-phenylethylamine and exhibiting good catalytic results have been reported [27, 28]. The authors believe that P/S ligands with an α-phenylethylamine framework should be useful in asymmetric catalytic reactions. Herein we synthesized a sulfur-aminophosphine ligand, L_1 (Fig. 1a), and a sulfur-phosphoramidite ligand, L_2 (Fig. 1b), based on α-phenylethylamine. The catalytic effects of the two ligands in C–C bond forming reactions were investigated. Furthermore, we compared the L_1, L_2 with bidedate phosphorous ligand L_3 (Fig. 1c) and ligand L_4, which was derived from ferrocene (Fig. 1d). The results showed that L_1 and L_2 displayed better enantioselectivity in the Pd-catalyzed allylic substitution and

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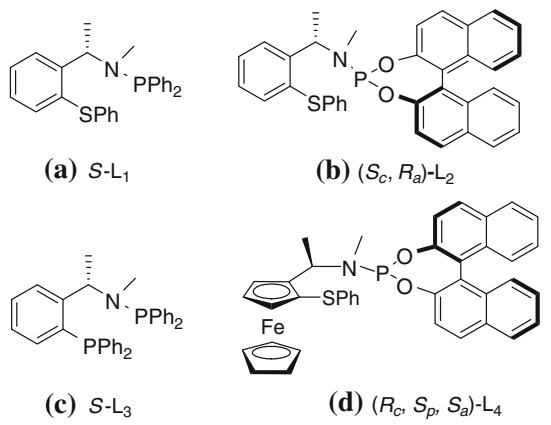


Fig. 1 The structure of ligands L_1, L_2, L_3 and L_4

Cu-catalyzed conjugated additions of cyclic enones, respectively.

2 Experimental

2.1 Chemicals and Apparatus

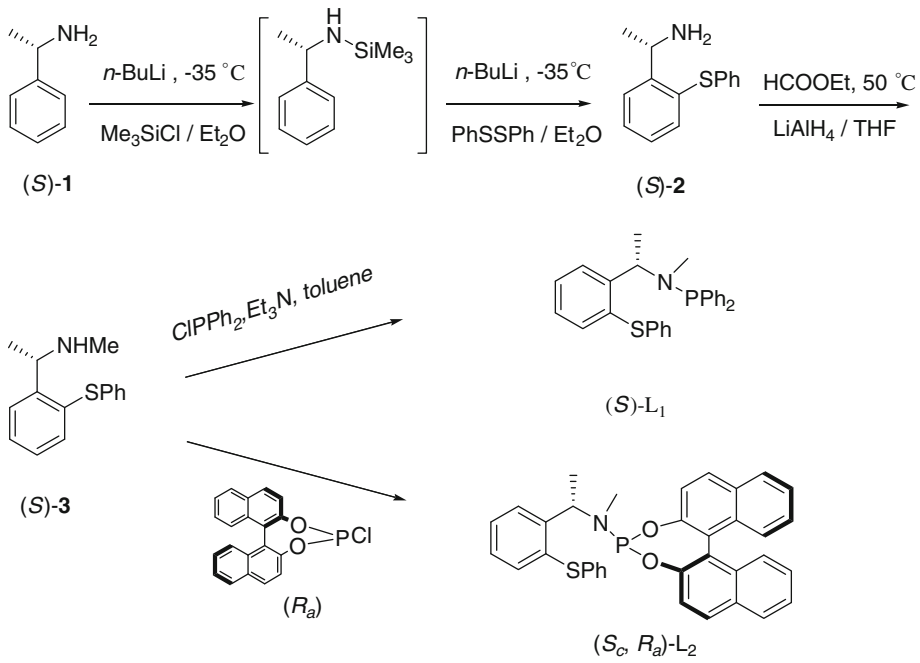
All synthetic reactions and manipulations were performed in nitrogen or argon atmosphere using standard Schlenk techniques. Solvents were reagent grade, dried, and distilled before use following the standard procedures. All raw materials were obtained commercially and used as received.

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on BRUKER DEX-400 spectrometer. Chemical shift values (δ) were denoted in ppm and were referenced to residue protons in deuterated solvents for ^{1}H NMR ($CDCl_3$: 7.27 ppm), to $CDCl_3$ (77.0 ppm) for ^{13}C NMR and to external H_3PO_4 (85% solution in D_2O, 0 ppm) for ^{31}P NMR. The enantiomeric excess of **8** was determined by HPLC (Chiralpak AD-H column (eluent:hexane/*i*-propanol = 90:10, 1.0 mL min^{-1}) and the absolute configuration was determined by comparing the retention times with literature. The enantiomeric excess of **10** was determined by GC analysis with chiral BGB-173 column (30 m × 0.25 mm × 0.25 μm). HRMS data were obtained with a Micromass HPLC-Q-TOF massspectrometer.

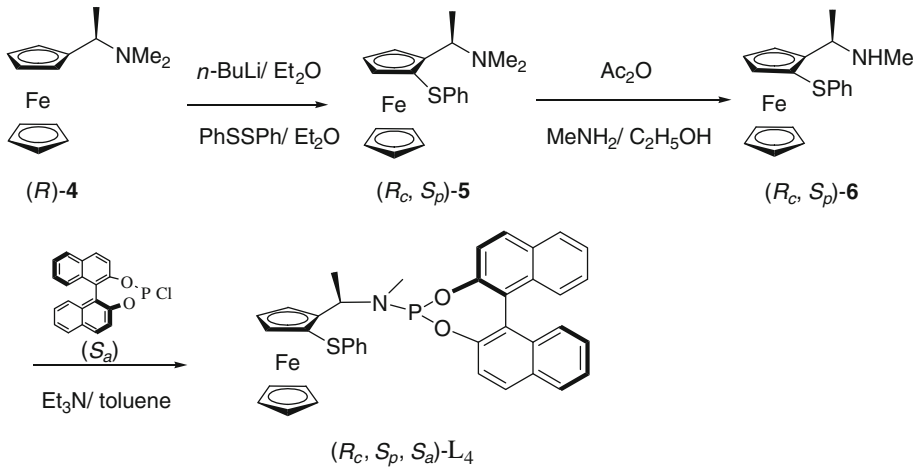
2.2 Synthesis of Ligands L_1, L_2 and L_4

L_1 and L_2 were easily prepared from α-phenylethylamine according to Scheme 1 [29]. The treatment of (*S*)-α-phenylethylamine with *n*-BuLi at −35 °C, followed by slow addition of neat Me_3SiCl generated the monosilylated product, *N*-(trimethylsilyl)-1-phenylethylamine. The latter was dilithiated by further addition of three equiv. of *n*-BuLi at −35 °C and then orthosulfonated with diphenyl disulfide. Following workup, (*S*)-**2** was produced in 45% overall yields. By treating with $HCOOC_2H_5$ at 40–50 °C and followed by reduction with $LiAlH_4$ in THF, (*S*)-**2** was monomethylated to form (*S*)-**3** in 76% yields. (*S*)-**3** can be easily converted to the corresponding sulfur-aminophosphine ligand L_1 and sulfur-phosphoramidite ligand L_2 in good yields by reaction with chlorodiphenylphophine and (R_a)-4-chloro-3,5-dioxa-4-phosphacyclohepta[2,1-α′;3,4-α′] dinaphthalene, respectively. The ligands L_1 and L_2 are not very sensitive to air and moisture.

Scheme 1 Synthesis of L_1 and L_2



Scheme 2 Synthesis of L_4



L_4 was synthesized from the chiral Ugi's amine following Scheme 2, which was similar to a reported method [30]. (*R*)-Ugi's amine was ortho-lithialated using *n*-BuLi/Et_2O, followed by quenching with diphenyl disulfide afforded the 1,2-disubstituted ferrocenyl amine **5** in 70% yields. Treatment of **5** with Ac_2O and methylamine in ethanol furnished the ferrocenyl methylamine **6** in 55% yields. The ferrocenylamine was then converted to the sulfur-phosphoramidite L_4 using Et_3N and (S_a)-4-chloro-3,5-dioxa-4-phosphacyclohepta[2,1-α';3,4-α']dinaphthalene.

Ligand L_3 was prepared in accordance to a known procedure [31].

2.3 Spectral Data for Ligands

(*S*)-L_1: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (d, $J = 6.9$ Hz, 3H), 2.31 (s, 3H), 5.01 (m, 1H), 7.15–7.45 (m, 19H); ^{31}P NMR ($CDCl_3$) δ 54.32; ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 33.8, 59.9, 126.7, 127.0, 127.4, 127.7, 127.8, 127.9, 128.0, 128.1, 128.5, 129.2, 130.9, 131.8, 132.0, 132.7, 132.9, 133.1, 136.6, 144.8. The ligand was not stable enough when it was in the HPLC-Q-TOF and just a very weak peak could be seen.

(S_c, R_a)-L_2: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (d, $J = 5.2$ Hz, 3H), 1.94 (d, $J = 2.4$ Hz, 3H), 5.18 (m, 1H), 7.22–7.92 (m, 21H); ^{31}P NMR ($CDCl_3$) δ 148.87; ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3, 28.7, 55.3, 122.0, 122.2, 124.5, 124.7, 126.0, 126.7, 127.0, 127.01, 127.5, 128.1, 128.2, 128.3, 129.2, 129.9, 130.2, 130.6, 133.9, 149.6. HRMS (EI) calcd. For $C_{35}H_{28}NO_2PS$ [M + H]: 558.1657, found 558.1681.

(R_c, S_p, S_a)-L_4: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76 (d, $J = 6.3$, 3H), 1.84 (s, 3H), 4.42 (s, 5H), 4.35–4.46 (m, 3H), 5.12-5.16 (m, 1H), 6.98-7.39 (m, 13H), 7.74-7.88 (m, 4H); ^{31}P NMR ($CDCl_3$) δ 148.93; ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 24.7, 50.0, 50.5, 68.7, 69.3, 70.5, 76.4, 77.1, 77.4, 121.9, 122.2, 124.3, 124.5, 125.4, 125.8, 125.9, 126.9, 128.2, 128.6, 129.8, 130.6, 132.6. HRMS (EI) calcd. For $C_{39}H_{32}FeNO_2PS$ [M + H]: 666.1319, found. 666.1345.

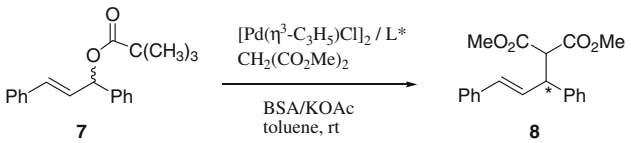
2.4 Typical Procedure of C–C Forming Reactions

2.4.1 Typical Procedure of Pd-Catalyzed Allylic Substitution Reaction

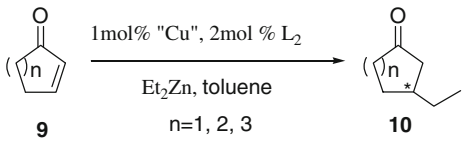
As described in Scheme 3, a solution of [Pd(η^3-C_3H_5)Cl]$_2$ (3.7 mg, 0.01 mmol) and chiral ligand (0.025 mmol) in toluene (1.5 mL) was stirred under argon atmosphere at room temperature for 1 h. To this Pd-catalyst was added allylic pivalate (0.5 mmol) in toluene (1.5 mL), followed by dimethyl malonate (0.17 mL, 1.5 mmol), *N*,*O*-*bis*(trimethysilyl)acetamide (BSA, 0.37 mL, 1.5 mmol), and a catalytic amount of base sequentially. After stirring at room temperature for 12 h, the reaction mixture was quenched with a saturated solution of aqueous NH_4Cl and diluted with CH_2Cl_2. The organic layer was evaporated under reduced pressure. The residue was purified by column chromatography (hexanes:ethyl acetate, 8:1) to afford the pure product.

2.4.2 Typical Procedure of Cu-Catalyzed Conjugated Additions of Cyclic Enones

As shown in Scheme 4, copper salt (0.005 mmol) was added to a ligand solution (0.011 mmol) in anhydrous toluene (1 mL). The resulting mixture was stirred under argon for 30 min at room temperature and then cooled to



Scheme 3 The Pd-catalyzed enantioselective allylic substitution reaction



Scheme 4 The enantioselective conjugated addition reaction

−30 °C. Substrate (0.5 mmol) and Et_2Zn (0.75 mmol, 1 M in toluene) were added. The mixture was stirred at −30 °C for 3 h and then quenched with saturated NH_4Cl solution (2 mL). The organic layer was washed with brine (2 mL), H_2O (2 mL) and dried over Na_2SO_4. The residue was purified by column chromatography (hexane) to afford the pure product.

3 Results and Discussions

3.1 Pd-Catalyzed Enantioselective Allylic Substitution Using Sulfur-Aminophosphine Ligands

In order to investigate the asymmetric catalytic efficiency of the prepared sulfur-phosphorus ligands, reaction of 1,3-diphenylprop-2-en-1-yl pivalate (**7**) with dimethyl malonate was chosen as model reaction. The results were summarized in Table 1. The results showed that L_1 exhibited good catalytic activity and moderate enantioselectivity with 96% yield and 74% ee, respectively (entry 1). However, L_2 showed poor enantioselectivity with only 8% ee (entry 2). Interestingly, L_3, the bidenate aminophosphine ligand similar to L_1, obtained inferior enantioselectivity with 37% ee (entry 3). These results indicated that the enantioselectivity of Pd-catalyzed asymmetric allylic substitution could be affected by the coordinating atoms. The heterodonor ligands equipped with weak and strong donor heteroatom pairs gave rise to different electronic properties, and could finetune the activity and enantioselectivity of asymmetric catalytic allylic alkylation [19]. On the other hand, it seems that the dimension of the groups linked to the coordinating atoms could also affect their enantioselectivity. Our experiments showed that L_4 which was derived from ferrocene exhibited worse enantioselectivity with only 26% ee (entry 4). Further investigation on this phenomenon is undertaking.

Table 1 Optimization of the reaction conditions of Pd-catalyzed enantioselective allylic substitution of 1,3-diphenylprop-2-en-1-yl pivalate (**7**)[a]

Entry	Ligand	Solvent	Base	ee (%)	Yield (%)[b]
1	L_1	Toluene	KOAc	74 (S)	96
2	L_2	Toluene	KOAc	8 (S)	96
3	L_3	Toluene	KOAc	37 (S)	91
4	L_4	Toluene	KOAc	26 (S)	83
5	L_1	THF	KOAc	44 (S)	86
6	L_1	DCM	KOAc	67 (S)	90
7	L_1	DMF	KOAc	60 (S)	80
8	L_1	Ether	KOAc	70 (S)	83
9	L_1	Toluene	NaOAc	74 (S)	93
10	L_1	Toluene	LiOAc	72 (S)	91
11	L_1	Toluene	CsOAc	72 (S)	94
12	L_1	Toluene	Cs_2CO_3	70 (S)	93

[a] The reaction was carried out at room temperature for 12 h in the presence of 2.0 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 5.0 mol% of ligand, 3.0 equiv. of dimethyl malonate, 3.0 equiv. of BSA and a catalytic amount of base

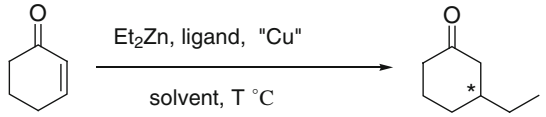
[b] Isolated yield

Then, L_1 was chosen as ligand and the reaction conditions were optimized. Initially, the influence of solvents was examined and significant variation in the catalytic enantioselectivity was observed. When the reaction was carried out in toluene, enantioselectivity with 74% ee was obtained (entry 1). But it was dramatically reduced in THF with only 44% ee (entry 5). The enantioselectivity was also slightly decreased when CH_2Cl_2 or DMF was used as solvent (entry 6, entry 7). However, using ether as solvent only had a little influence on enantioselectivity (entry 8). Next, the effects of base additives on the catalytic reaction were evaluated using toluene as solvent. It seems that the enantioselectivity did not strongly depend on base additive, and in all base conditions, moderate results were obtained (entries 9–12). However, the base additives could affect the catalytic activity. When KOAc and NaOAc were compared, the same enantioselectivity was obtained (74% ee), but KOAc showed more positive effect on the catalytic activity (entry 1 versus entry 9). Based on the experiment results mentioned above, we concluded that L_1 shows the best enantioselectivity and catalytic activity in the Pd-catalyzed enantioselective allylic substitution, and toluene should be selected as solvent while KOAc as base additives.

3.2 Cu-Catalyzed Conjugated Additions of Cyclic Enones with Sulfur-Phosphoramidite L_2

Though L_2 was ineffective in the Pd-catalyzed asymmetric allylic substitution, we found it was useful in asymmetric copper-catalyzed conjugated addition of diethylzinc on 2-cyclohexenone (Scheme 4). First, the reaction was carried out at −30 °C with 2% mol of $Cu(OTf)_2$ and 5% mol of ligand, and some familiar solvents were examined. The results were summarized in Table 2. When toluene was applied as solvent, the substrate was thoroughly converted within 3 h with 73% ee (entry 1). In THF, the catalytic activity was sharply decreased with only 43% conversion and 65% ee were obtained (entry 2). Furthermore, in CH_2Cl_2, the enantioselectivity was as low as 20% ee (entry 3).

Table 2 Optimization of the enantioselective conjugated addition reaction conditions with ligand L_2

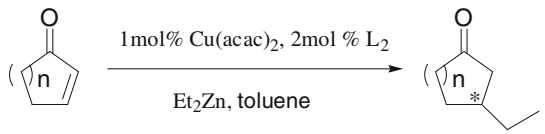


Entry	Solvent	Temp (°C)	Cu complex	Catalyst (%)	ee (%)	Yield (%)[a]
1	Toluene	−30	$Cu(OTf)_2$	2	73 (S)	100
2	THF	−30	$Cu(OTf)_2$	2	65 (S)	43
3	DCM	−30	$Cu(OTf)_2$	2	20 (S)	90
4	Ether	−30	$Cu(OTf)_2$	2	65 (S)	97
5	Toluene	−15	$Cu(OTf)_2$	2	70 (S)	100
6	Toluene	0	$Cu(OTf)_2$	2	70 (S)	100
7	Toluene	RT	$Cu(OTf)_2$	2	68 (S)	100
8	Toluene	−30	$CuSO_4{\cdot}5H_2O$	2	12 (S)	20
9	Toluene	−30	CuI	2	45 (S)	30
10	Toluene	−30	Cu_2Cl_2	2	67 (S)	97
11	Toluene	−30	$CuCl_2$	2	70 (S)	78
12	Toluene	−30	$Cu(OAc)_2{\cdot}H_2O$	2	75 (S)	100
13	Toluene	−30	$Cu(acac)_2$	2	76 (S)	100
14	Toluene	−30	$Cu(acac)_2$	1	76 (S)	95
15	Toluene	−30	$Cu(acac)_2$	0.5	72 (S)	84
16	Toluene	−30	$Cu(acac)_2$	3	76 (S)	100

[a] Isolated yield

When ether was used as solvent, the catalytic activity and enantioselectivity exhibited a little lower compared to toluene (entry 4). Then, we explored the influence of temperature. We found that the reaction temperature shown negligible effect on the conjugated addition reaction (entries 5–7). Later, we found the precatalyst had critical influence on the reaction. $CuSO_4{\cdot}5H_2O$ and CuI were not suitable to the asymmetric catalytic reaction which resulted in low ee and low conversion (entry 8, entry 9). Using Cu_2Cl_2 and $CuCl_2$ as precatalyst, moderate results were obtained with 67% ee, 97% conversion and 70% ee, 98% conversion (entry 10, entry 11), respectively. The enantioselectivity was improved by $Cu(OAc)_2{\cdot}H_2O$ and $Cu(acac)_2$ (entry 12, entry 13). The optimal ee reached to 76% with full conversion using $Cu(acac)_2$ as precatalyst. When $Cu(acac)_2$ was reduced to 1% equiv. of cyclohexanone, the enantioselectivity could hold in 76% with 95% conversion (entry 14). The catalytic activity and enantioselectivity were decreased with 0.5% equiv. $Cu(acac)_2$ (entry 15). However, no better result was obtained as the quantity of the catalyst was enhanced (entry 16). Based on the above optimized experiments, we concluded that toluene was the best solvent and $Cu(acac)_2$ as precatalyst was more suitable to the enantioselective conjugated addition reaction with 1% catalyst.

Table 3 Enantioselective conjugated addition of diethylzinc to cyclic enones with ligand L_2[a]



Entry	*n*	Temp (°C)	ee (%)	Yield (%)[b]
1	1	−30	25 (S)	65
2	1	−15	20 (S)	83
3	1	0	17 (S)	96
4	1	RT	13 (S)	99
5	2	−30	76 (S)	95
6	2	−15	76 (S)	99
7	2	0	73 (S)	99
8	2	RT	68 (S)	100
9	3	−30	73 (S)	77
10	3	−15	73 (S)	77
11	3	0	70 (S)	80
12	3	RT	65 (S)	92

[a] The reaction was carried out in the toluene for 3 h in the presence of 1.0 mol% of $Cu(acac)_2$, 2.0 mol% of ligand L_2, 1.5 equiv. of Et_2Zn

[b] Isolated yield

Under the optimal conditions, we explored the enantioselective conjugated addition reaction of cyclic enones with $Cu(acac)_2$ at different temperature (Table 3). When cyclopentenone was used as substrate, the enantioselectivity was quite low. The catalytic activity was gently improved when the temperature was risen (entries 1–4). Addition of Et_2Zn to cyclohexenone with $Cu(acac)_2$ could obtain better catalytic activity and enantioselectivity. The highest ee reached 76% with 99% yield at −15 °C (entries 5–8). However, for 2-cycloheptenone the catalytic activity was moderate despite enhancing the reaction temperature, and the optimal enantioselectivity was 73% below 0 °C (entries 8–10). The ee value was reduced with enhancing the reaction temperature (entries 11, 12).

4 Conclusion

In conclusion, we have developed a new family of chiral P/S ligands L_1, L_2 and L_4. Good reactivities and moderate enantioselectivities were obtained in the Pd-catalyzed allylic substitution with L_1 and Cu-catalyzed conjugated additions of cyclic enones with L_2. Further investigation of other P/S ligands applied in asymmetric catalytic reactions is underway.

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