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Novel chiral phosphine–oxazinane ligands in palladium-catalyzed asymmetric allylic alkylation

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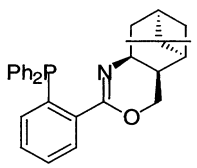
Abstract—Palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**8a**) with a dimethyl malonate–BSA–LiOAc system has been successfully carried out in the presence of novel chiral phosphine–oxazinane ligands such as **5b** in good yields with good enantioselectivities (up to 95% ee). © 2001 Elsevier Science Ltd. All rights reserved.

Palladium-catalyzed asymmetric allylic alkylation is a useful process for asymmetric C–C bond forming reactions. To achieve high enantioselectivity in the catalytic reaction, a variety of chiral ligands have been studied.[1] Among the ligands, chiral oxazolines have proved to be extremely efficient ligands in some catalytic reactions.[2] Recently, chiral phosphine–oxazine ligand **1**[3] and chiral phosphine–oxazolidine ligands **2**[4] and **3**[5] were shown to be effective ligands in palladium-catalyzed asymmetric allylic alkylation similarly to phosphine–oxazolines. On the other hand, palladium-catalyzed asymmetric allylic alkylation using phosphine–oxathiane ligand **4** has been reported.[6] To the best of our knowledge, the oxazinane type ligands have never been involved in this area. With the aim of exploiting the less popular oxazinanes, we synthesized chiral phosphine–oxazinane, starting from (*S*)-ketopinic acid.[7] Herein, we wish to describe the first application of the oxazinanes as ligands to the palladium-catalyzed asymmetric allylic alkylation.



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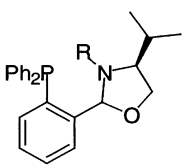

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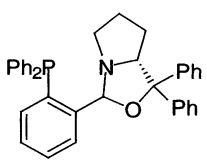

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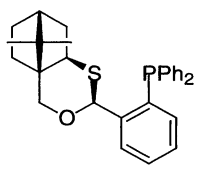

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The synthesis of phosphine–oxazinane ligands **5** is shown in Scheme 1 and Table 1. These ligands **5**[8] were prepared by the corresponding amines with (*S*)-ketopinic acid followed by the reduction of **6**, and the condensation of aminoalcohols **7** with 2-(diphenylphosphino)benzaldehyde.

The ligands **5** were obtained the diasteromerically pure within NMR spectra. The stereochemistry of **5b** was determined by NOE measurement of ^{1}H NMR spectra. Thus, the NOE experiment for **5b** confirmed interactions between the H^a and H^b and between H^b and H^c (Fig. 1).

We applied the chiral phosphine–oxazinane ligands **5** to the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**8a**) with a dimethyl malonate (**9a**) (Scheme 2). This reaction was carried out in the presence of 2 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 4 mol% of chiral ligand, and a mixture of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and 2 mol% of LiOAc at room temperature (entries 1–4, Table 2). These ligands **5** showed similar reactivity and enantioselectivity except **5d**. Using ligand **5b**, the product (*R*)-**10a** was obtained the best enantioselectivity (79% ee) in these ligands **5** (entry 2). We investigated the effect of solvents on this reaction using **5b** (entries 2 and 5, 6, 8). When the reaction was carried out in toluene, the enantioselectivity was higher than for the other solvents (entry 6). On

Keywords: asymmetric synthesis; phosphine; oxazinane; palladium.
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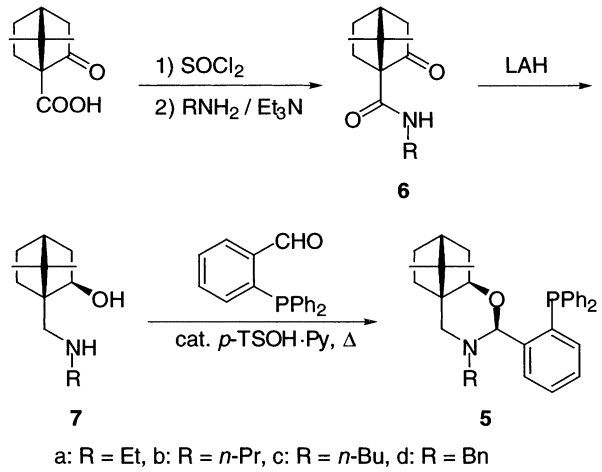


Scheme 1.

Table 1. Synthesis of phosphine–oxazinane ligands **5**

Entry	R	Yield of **6** (%)	Yield of **7** (%)	Yield of **5** (%)
1	Et	36	59	55
2	*n*-Pr	58	90	47
3	*n*-Bu	65	65	64
4	Bn	52	6	38

the other hand, with diethyl methylmalonate (**9c**), the reaction gave the corresponding product **10c**[9] in moderate enantioselectivity (entry 7). The reaction at 0°C further improved the enantioselectivity to 88% ee (entry 9). Although the reaction rate became slow by further depressing the temperature (−20°C), the enantioselectivity was improved to 95% ee (entry 10). When 1,3-diphenyl-2-propenyl pivalate (**8b**) was used instead of 1,3-diphenyl-2-propenyl acetate (**8a**), the reaction with a dimethyl malonate (**9a**) gave the product **10a** in good enantioselectivity (entry 11). When diethyl malonate (**9b**) was used instead of **9a**, the reaction gave the corresponding product **10b**[10] in good enantioselectivity (entry 12).

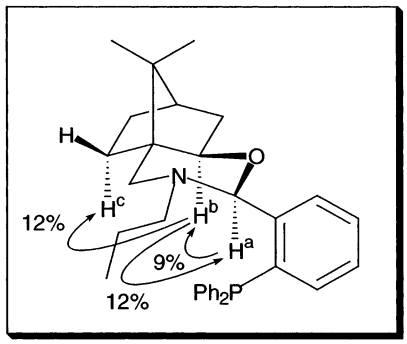
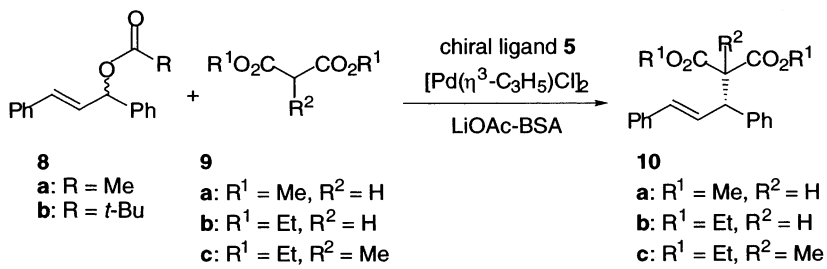


Figure 1. Selected NOE correlations of **5b**.



Scheme 2.

Table 2. Asymmetric allylic alkylation using chiral ligands **5**[a]

Entry	Ligand	R	R^1	R^2	Solv.	Temp. (°C)	Yield of **10** (%)[b]	Ee of **10** (%)[c]
1	**5a**	Me	Me	H	THF	rt	85	64
2	**5b**	Me	Me	H	THF	rt	98	79
3	**5c**	Me	Me	H	THF	rt	82	74
4	**5d**	Me	Me	H	THF	rt	13	22
5	**5b**	Me	Me	H	Ether	rt	87	80
6	**5b**	Me	Me	H	PhMe	rt	81	85
7	**5b**	Me	Et	Me	PhMe	rt	59	60
8	**5b**	Me	Me	H	MeCN	rt	47	65
9[d]	**5b**	Me	Me	H	PhMe	0	90	88
10[d]	**5b**	Me	Me	H	PhMe	−20	50	95
11[e]	**5b**	*t*-Bu	Me	H	PhMe	−20	20	95
12[e]	**5b**	Me	Et	H	PhMe	−20	73	92[f]

[a] The reaction was carried out for 24 h.
[b] Isolated yields.
[c] Determined by HPLC analysis using a chiral column (Chiralcel OD-H).
[d] This reaction was carried out for 100 h.
[e] This reaction was carried out for 120 h.
[f] Determined by HPLC analysis using a chiral column (Chiralcel OJ).

In conclusion, we have prepared novel chiral phosphine–oxazinane such as **5b** and demonstrated the palladium-catalyzed asymmetric allylic alkylation proceeded using these ligands with a good enantiomeric excess of up to 95% ee. Further application and modification of the ligand **5** are in progress.

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8. Selected data for **5a**: $[\alpha]_D^{20}=-39.0°$ (*c* 0.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, 7.1 Hz, 3H), 0.83–1.02 (m, 2H), 0.90 (s, 3H), 1.34–1.69 (m, 5H), 1.39 (s, 3H), 1.76–1.84 (m, 1H), 2.09 (d, 12.2 Hz, 1H), 2.13–2.22 (m, 1H), 3.12 (d, 12.2 Hz, 1H), 3.28 (dd, 2.9 and 7.8 Hz, 1H), 5.22 (d, 7.1 Hz, 1H), 6.83–6.85 (m, 1H), 7.17–7.18 (m, 1H), 7.25–7.36 (m, 11H), 7.73–7.77 (m, 1H); ^{31}P NMR (122 MHz, $CDCl_3$) δ −15.9; FAB-MS (*m*/*z*) 468 (M^+−H, 70); HRMS (FAB) calcd for $C_{31}H_{36}NOP$+H 470.2613, found 470.2595
   Selected data for **5b**: $[\alpha]_D^{20}=-50.3°$ (*c* 0.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.68 (t, 6.9 Hz, 3H), 0.83–0.87 (m, 1H), 0.90 (s, 3H), 0.94–0.98 (m, 1H), 1.21–1.34 (m, 3H), 1.36–1.42 (m, 1H), 1.41 (s, 3H), 1.50 (dd, 7.9 and 13.3 Hz, 1H), 1.60–1.72 (m, 2H), 1.77–1.84 (m, 1H), 1.98–2.03 (m, 1H), 2.05 (d, 12.2 Hz, 1H), 3.10 (d, 12.2 Hz, 1H), 3.32 (dd, 2.8 and 7.8 Hz, 1H), 5.23 (d, 7.1 Hz, 1H), 6.84–6.85 (m, 1H), 7.17–7.19 (m, 1H), 7.26–7.38 (m, 11H), 7.73–7.76 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.52, 20.05, 20.54, 22.69, 26.96, 31.16, 37.39, 45.59, 46.08, 46.20, 52.27, 53.84, 83.13, 92.00 (d, 26.9 Hz), 128.21–128.54 (Ar, m), 128.83, 129.41, 132.83, 133.77 (d, 19.7 Hz), 134.70 (d, 20.7 Hz), 135.86 (d, 14.5 Hz), 136.45 (d, 10.5 Hz), 136.90 (d, 10.3 Hz), 144.98 (d, 20.7 Hz); ^{31}P NMR (122 MHz, $CDCl_3$) δ −16.0; FAB-MS (*m*/*z*) 482 (M^+−H, 27); HRMS (FAB) calcd for $C_{32}H_{38}NOP$+H 484.2768, found 484.2735.
   Selected data for **5c**: $[\alpha]_D^{20}=-41.5°$ (*c* 0.11, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.72 (t, 7.3 Hz, 3H), 0.90 (s, 3H), 0.94–1.68 (m, 8H), 1.41 (s, 3H), 1.78–1.84 (m, 1H), 2.01–2.09 (m, 1H), 2.04 (d, 12.1 Hz, 1H), 2.17 (br, 3H), 3.10 (d, 12.2 Hz, 1H), 3.32 (dd, 2.8 and 7.8 Hz, 1H), 5.23 (d, 7.1 Hz, 1H), 6.84–6.87 (m, 1H), 7.17–7.19 (m, 1H), 7.26–7.36 (m, 11H), 7.72–7.74 (m, 1H); ^{31}P NMR (122 MHz, $CDCl_3$) δ −16.1; FAB-MS (*m*/*z*) 496 (M^+−H, 97); HRMS (FAB) calcd for $C_{33}H_{40}NOP$+H 498.2926, found 498.2878.
   Selected data for **5d**: $[\alpha]_D^{20}=-156.0°$ (*c* 0.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H), 0.86–0.92 (m, 2H), 1.23–1.28 (m, 4H), 1.52 (s, 3H), 1.57–1.59 (m, 1H), 2.52–2.57 (m, 1H), 3.02 (d, 14.3 Hz, 1H), 3.10 (d, 12.3 Hz, 1H), 3.68 (d, 14.3 Hz, 1H), 3.79 (d, 12.3 Hz, 1H), 5.19 (d, 6.9 Hz, 1H), 6.74–6.75 (m, 1H), 7.07–7.10 (m, 6H), 7.23–7.36 (m, 11H), 7.75–7.82 (m, 1H); ^{31}P NMR (122 MHz, $CDCl_3$) δ −14.4; FAB-MS (*m*/*z*) 530 (M^+−H, 18); HRMS (FAB) calcd for $C_{36}H_{38}NOP$+H 532.2769, found 532.2747.
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