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Remote substituent effect in palladium/pyridinyl-oxazolines catalyzed asymmetric allylic alkylation

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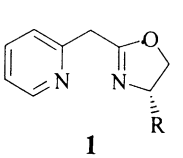
Abstract

The chiral ligands containing pyridinyl moieties and oxazolines bridged by disubstituted methylene **2**–**4** were prepared and they provided ee values 17–68% higher than unsubstituted analogues **1** in the palladium-catalyzed enantioselective allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate.

Keywords: Chiral ligand; Enantioselectivity; Allylic alkylation

1. Introduction

Recently, we introduced chiral bidentate nitrogen ligands that contain pyridine or quinoline moieties and the oxazolines for the investigation on the influence of the chelate ring size in the Cu-catalyzed enantioselective cyclopropanation of styrene with diazo acetates [1]. At almost the same time, Chelucci et al. [2] reported that pyridinylmethyl-oxazolines **1**, initially developed by Fryzuk et al. [3], could be used as ligands in the palladium-catalyzed allylic alkylation reaction, however, the enantioselectivities were rather poor. Being interested in whether the introduction of substituents on the methylene bridge in ligands **1** will affect the structure of palladium catalyst and improve the enantioselectivity of allylic alkylation reaction, we synthesized dialkyl methylene bridged pyridinyl-oxazoline ligands **2**–**4**. In this paper, we would like to describe our results of the investigation on the ligands **2**–**4** in palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate.



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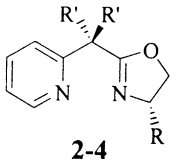

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2. Experimental

2.1. General

DMSO was distilled from CaH_2 under reduced pressure. Xylene was distilled from Na/benzophenone. All optically pure amino alcohols were prepared by reductions of the corresponding commercially available

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amino acids with $NaBH_4/I_2$ in THF. Ligands **2** were prepared by the method described in previous paper [1b]. IR (film): selected bands in cm^{-1}. ^1H NMR ($CDCl_3$, 300 or 500 MHz): δ in ppm (TMS), J in Hz. MS (EI): selected peaks, m/z (%).

2.2. Synthesis of ethyl pyridinylacetates (*5*)

2.2.1. Ethyl 2-ethyl-2-(2′-pyridinyl)butyrate

General procedure: NaH (0.48 g, 20 mmol) was suspended in 15 ml anhydrous DMSO and stirred for 30 min. Ethyl (2′-pyridyl)acetate (0.83 g, 5.03 mmol) was added dropwise, then 2.34 g (1.2 ml, 15 mmol) ethyl iodide was slowly added during 1 h. The mixture was stirred at room temperature for 10 h and was poured into 60 ml water. The solution was extracted with dichloromethane (3× 50 ml). The combined organic layer was washed with water (4× 50 ml) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with petroleum ether:EtOAc (4:1) to give 0.92 g (4.16 mmol, 83%) of titled product as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.57 (d, $J = 4.8$ Hz, 1H), 7.64 (t, $J = 7.8$ Hz, 1H), 7.24 (d, $J = 7.8$ Hz, 1H), 7.14 (dd, $J = 7.8$ and 4.8 Hz, 1H), 4.16 (q, $J = 7.2$ Hz, 2H), 2.13 (q, $J = 7.5$ Hz, 4H), 1.17 (t, $J = 7.2$ Hz, 3H), 0.74 (t, $J = 7.5$ Hz, 6H). IR: 3053w, 2971m, 2879w, 1731s, 1487s, 1223s, 1138s, 1109s. MS: 222 (M^+, 100), 193 (45), 178 (73), 160 (40), 148 (90), 132 (53), 118 (49).

2.2.2. Ethyl 2-butyl-2-(2′-pyridinyl)caproate

Colorless oil, 72% yield. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.61 (d, $J = 4.8$ Hz, 1H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.25 (d, $J = 7.4$ Hz, 1H), 7.12 (dd, $J = 7.4$ and 4.8 Hz, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 2.01 (t, $J = 7.8$ Hz, 4H), 0.99–1.45 (m, 11H), 0.77–0.84 (m, 6H). IR: 3456w, 3084m, 3084m, 3029s, 2979m, 2857w, 1737s, 1494s, 1370s, 1221s, 1019s, 963s. MS: 210 (29), 193 (75), 192 (100), 191 (77), 115 (40), 105 (33).

2.3. Synthesis of pyridinylacetamides (*6*)

2.3.1. (1′S)-N-(1′-Isopropyl-2′-hydroxylethyl)-2-ethyl-2-(2′-pyridinyl)butyramide

General procedure: Ten milliliters of xylene, 0.92 g (4.16 mmol) of ethyl 2-ethyl-2-(2′-pyridinyl)butyrate, 0.64 g (6.21 mmol) (*S*)-2-amino-3-methyl-1-butanol and 0.05 g (1.02 mmol) NaCN were added into a 100 ml Schlenk tube successively under argon. The mixture was refluxed for 72 h with weak nitrogen flow. After cooled to room temperature, 60 ml chloroform was added in. The solution was washed with water (2× 20 ml) and brine, dried with anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel with petroleum ether:EtOAc (1:1) to give 0.72 g (2.59 mmol, 62%) of titled compound as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.53 (d, $J = 4.8$ Hz, 1H), 8.29 (s, 1H), 7.72 (t, $J = 7.5$ Hz, 1H), 7.42 (d, $J = 7.5$ Hz, 1H), 7.19 (dd, $J = 7.5$ and 4.8 Hz, 1H), 3.71–3.85 (m, 2H), 3.55–3.65 (m, 2H), 1.81–2.24 (m, 5H), 0.96 (d, $J = 7.1$ Hz, 3H), 0.93 (d, $J = 7.1$ Hz, 3H), 0.75 (t, $J = 7.3$ Hz, 6H). IR: 3369s, 3053m, 2964s, 2935s, 2876s, 1644s, 1525s, 1466s, 1385s, 1073s. MS: 279 (M^+, 100), 261 (22), 247 (8), 176 (6), 148 (29), 134 (12), 117 (5).

2.3.2. (1′S)-N-(1′-tert-Butyl-2′-hydroxylethyl)-2-ethyl-2-(2′-pyridinyl)butyramide

Colorless oil, 46% yield. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.60 (s, 1H), 8.52 (d, $J = 4.9$ Hz, 1H), 7.73 (t, $J = 7.7$ Hz, 1H), 7.41 (d, $J = 7.7$ Hz, 1H), 7.19 (dd, $J = 7.7$ and 4.9 Hz, 1H), 3.82–3.93 (m, 3H), 3.45–3.56 (m, 1H), 1.95–2.27 (m, 4H), 0.96 (s, 9H), 0.70–0.83 (m, 6H). IR: 3422s, 3053m, 2965s, 2877s, 1727w, 1648s, 1590s, 1523s, 1470s, 1431s, 1366m, 1257m, 1156w, 1052m, 999m. MS: 235 (12), 176 (27), 148 (100), 134 (41), 118 (12), 106 (12).

2.3.3. (1′S)-N-(1′-Isopropyl-2′-hydroxylethyl)-2-butyl-2-(2′-pyridinyl)caproamide

Colorless oil, 58% yield. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.52 (s, 1H), 8.31 (d, $J = 4.8$ Hz, 1H), 7.72 (t, $J = 7.8$ Hz, 1H), 7.41 (d, $J = 7.8$ Hz, 1H), 7.70 (dd, $J = 7.8$ and 4.8 Hz, 1H), 3.76–3.88 (m, 2H), 3.67–3.76 (m, 1H), 3.17–3.28 (m, 1H), 1.86–2.18 (m, 5H), 1.19–1.31 (m, 4H), 1.01–1.17 (m, 4H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H), 0.83 (t, $J = 7.3$ Hz, 6H). IR: 3395m, 3052m, 2957s, 2871s, 2732w, 1644s, 1590s, 1525s, 1466s, 1431s, 1369m, 1075m, 1054m. MS: 335 (50), 232 (10), 204 (100), 162 (57), 132 (12), 106 (15).

2.3.4. (1′S)-N-(1′-tert-Butyl-2′-hydroxylethyl)-2-butyl-2-(2′-pyridinyl)caproamide

Colorless oil, 38% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.54 (s, 1H), 8.51 (d, $J = 5.9$ Hz, 1H), 7.72 (t, $J = 7.8$ Hz, 1H), 7.41 (d, $J = 7.8$ Hz, 1H), 7.19 (dd, $J = 7.8$ and 5.9 Hz, 1H), 3.85–3.92 (m, 3H), 3.46–3.52 (m, 1H), 2.13–2.22 (m, 2H), 1.87–1.95 (m, 2H), 1.22–1.30 (m, 4H), 1.01–1.19 (m, 4H), 0.94 (s, 9H), 0.72–0.98 (m, 6H). IR: 3426m, 3195w, 3052w, 2957s, 2871s, 1654s, 1571s, 1467s, 1471s, 1366m, 1260m, 1052m, 1001m. MS: 331 (2), 232 (15), 204 (100), 162 (38), 106 (10).

*2.4. Synthesis of pyridinylacetamides (**7**)*

2.4.1. (1′S)-N-(1′-Isopropyl-2′-chloroethyl)-2-ethyl-2-(2′-pyridinyl)butyramide

General procedure: A solution of 1.54 g (0.94 ml, 12.94 mmol) $SOCl_2$ in 10 ml chloroform was added dropwise into a 50 ml three-necked flask, which contented 0.72 g (2.59 mmol) of (1′*S*)-*N*-(1′-isopropyl-2′-hydroxylethyl)-2-ethyl-2-(2′-pyridinyl)butyramide and 25 ml chloroform, during 30 min. The resulting solution was refluxed for 1 h and 10 ml water was added slowly after the solution cooled to room temperature. The layers were separated, and the water phase was neutralized with saturated $NaHCO_3$ and extracted with chloroform (2× 30 ml). The organic phases were combined and washed with 25 ml water, dried with anhydrous Na_2SO_4. Concentration and column chromatography on silica gel with petroleum ether:EtOAc (4:1) gave 0.66 g (2.23 mmol, 86%) of titled product as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.56 (s, 1H), 8.31 (d, $J = 4.8$ Hz, 1H), 7.77 (t, $J = 7.5$ Hz, 1H), 7.43 (d, $J = 7.5$ Hz, 1H), 7.25 (dd, $J = 7.5$ and 4.8 Hz, 1H), 3.56–3.92 (m, 2H), 1.85–2.34 (m, 6H), 0.96 (d, $J = 7.1$ Hz, 3H), 0.93 (d, $J = 7.1$ Hz, 3H), 0.79 (t, $J = 7.3$ Hz, 6H). IR: 3385m, 2967s, 2878s, 2577m, 2045w, 1738s, 1589s, 1571m, 1468s, 1380m, 1216s, 1139s, 1002m. MS: 261 (25), 235 (23), 194 (23), 192 (34), 148 (100), 134 (33), 106 (16).

2.4.2. (1′S)-N-(1′-tert-Butyl-2′-chloroethyl)-2-ethyl-2-(2′-pyridinyl)butyramide

Colorless oil, 98% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.57 (s, 1H), 8.49 (d, $J = 4.9$ Hz, 1H), 7.69 (t, $J = 7.8$ Hz, 1H), 7.27 (d, $J = 7.8$ Hz, 1H), 7.15 (dd, $J = 7.8$ and 4.9 Hz, 1H), 4.40–4.67 (m, 3H), 1.94–2.09 (m, 4H), 0.74–0.83 (m, 15H). IR: 3366w, 2966s, 2878s, 2626m, 2546m, 2051w, 1738s, 1659s, 1589s, 1525s, 1470s, 1378m, 1216s, 1136s, 1108s. MS: 235 (39), 217 (32), 192 (14), 176 (19), 148 (100), 134 (15).

2.4.3. (1′S)-N-(1′-Isopropyl-2′-chloroethyl)-2-butyl-2-(2′-pyridinyl)caproamide

Colorless oil, 64% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.54 (d, $J = 4.8$ Hz, 1H), 8.38 (s, 1H), 7.75 (t, $J = 7.8$ Hz, 1H), 7.50 (d, $J = 7.8$ Hz, 1H), 7.68 (dd, $J = 7.8$ and 4.8 Hz, 1H), 3.56–3.82 (m, 3H), 1.88–2.25 (m, 5H), 1.32–1.55 (m, 4H), 1.12–1.24 (m, 4H), 0.98 (d, $J = 6.9$ Hz, 3H), 0.93 (d, $J = 6.9$ Hz, 3H), 0.87 (t, $J = 7.4$ Hz, 6H). IR: 3358w, 3050m, 2957s, 2871s, 1738m, 1656s, 1589s, 1467s, 1431s, 1378m, 1244m, 1198m. MS: 353 (M^+, 10), 317 (56), 273 (47), 217 (92), 204 (100), 162 (51).

2.4.4. (1′S)-N-(1′-tert-Butyl-2′-chloroethyl)-2-butyl-2-(2′-pyridinyl)caproamide

Colorless oil, 76% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.56 (s, 1H), 8.20 (d, $J = 5.9$ Hz, 1H), 7.67 (t, $J = 7.7$ 1H), 7.40 (d, $J = 7.7$ Hz, 1H), 7.17 (dd, $J = 7.7$ and 5.9 Hz, 1H), 3.90–4.14 (m, 3H), 2.01–2.13 (m, 4H), 1.25–1.32 (m, 4H), 1.04–1.10 (m, 4H), 0.88 (s, 9H), 0.82–0.86 (m, 6H). IR: 3160w, 2956s, 2870s, 1738m, 1658s, 1589s, 1467s, 1431m, 1367m, 1197m. MS: 367 (M^+, 33), 331 (100), 273 (32), 231 (33), 204 (58).

*2.5. Synthesis of pyridinylmethyl-oxazolines (**3** and **4**)*

*2.5.1. (4S)-4,5-Dihydro-2-(1′-ethyl-1′-(2′-pyridinyl)propyl)-4-isopropyloxazole (**3b**)*

General procedure: (1′*S*)-*N*-(1′-Isopropyl-2′-chloroethyl)-2-ethyl-2-(2′-pyridinyl)butyramide (380 mg, 1.28 mmol) and 77 mg NaOH was dissolved in 20 ml anhydrous methanol. The solution was refluxed for 20 h. After most of the solvent was removed, 20 ml water was added, and the mixture was extracted with dichloromethane (2× 250 ml). Usual work-up and column chromatography on silica gel with petroleum ether:EtOAc (2:1) gave 0.28 g (1.08 mmol, 75%) of **3b** as a colorless oil. $[\alpha]_D^{20} = 152$ (c 1.0, EtOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.51 (d, $J = 4.7$ Hz, 1H), 7.55 (t, $J = 7.7$ Hz, 1H), 7.25 (d, $J = 7.7$ Hz,

1H), 7.06 (dd, $J = 7.7$ and 4.7 Hz, 1H), 4.07 (t, $J = 8.0$ Hz, 1H), 3.85–3.97 (m, 1H), 3.84 (t, $J = 8.0$ Hz, 1H), 1.96–2.11 (m, 4H), 1.70–1.83 (m, 1H), 0.92 (d, $J = 6.8$ Hz, 3H), 0.81 (d, $J = 6.8$ Hz, 3H), 0.60–0.77 (m, 6H). IR: 3292w, 3061m, 2964s, 2876s, 2737w, 1737w, 1657s, 1588s, 1469s, 1383m, 1266m, 1219s. MS: 261 (M^+, 100), 245 (30), 232 (68), 217 (96), 189 (65), 159 (26), 117 (27). HRMS ($C_{16}H_{24}N_2O$): calcd., 260.1888; found, 260.1876.

*2.5.2. (4S)-4,5-Dihydro-2-(1′-ethyl-1′-(2′-pyridinyl)propyl)-4-tert-butyloxazole (**3d**)*

Colorless oil, 84% yield. $[\alpha]_D^{20} = 115$ (c 1.0, EtOH). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.57 (d, $J = 4.7$ Hz, 1H), 7.62 (t, $J = 8.1$ Hz, 1H), 7.34 (d, $J = 8.1$ Hz, 1H), 7.11 (dd, $J = 8.1$ and 4.7 Hz, 1H), 3.83–4.12 (m, 3H), 2.13–2.72 (m, 4H), 0.93 (s, 9H), 0.70–0.79 (m, 6H). IR: 3061w, 2963s, 2903m, 2877m, 2741w, 1659s, 1588s, 1569m, 1469s, 1430m, 1363m, 1219m, 1130m. MS: 273 (100), 245 (84), 233 (87), 189 (92), 131 (58). HRMS ($C_{17}H_{26}N_2O$): calcd., 274.2045; found, 274.2031.

*2.5.3. (4S)-4,5-Dihydro-2-(1′-butyl-1′-(2′-pyridinyl)-amyl)-4-isopropyloxazole (**4b**)*

Colorless oil, 71% yield. $[\alpha]_D^{20} = 139$ (c 1.0, EtOH). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.60 (d, $J = 4.6$ Hz, 1H), 7.63 (t, $J = 7.7$ Hz, 1H), 7.34 (d, $J = 7.7$ Hz, 1H), 7.15 (dd, $J = 7.7$ and 4.6 Hz, 1H), 4.14 (t, $J = 8.4$ Hz, 1H), 3.95–4.11 (m, 1H), 3.92 (t, $J = 8.4$ Hz, 1H), 2.04–2.24 (m, 4H), 1.66–1.92 (m, 1H), 1.20–1.36 (m, 4H), 1.09–1.18 (m, 4H), 1.08 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H), 0.87 (t, $J = 7.3$ Hz, 6H). IR: 2957s, 2872s, 1656s, 1588s, 1569m, 1467s, 1429s, 1199m, 1119m. MS: 316 (M^+, 5), 272 (39), 260 (20), 217 (100), 131 (18). HRMS ($C_{20}H_{32}N_2O$): calcd., 316.2514; found, 316.2510.

*2.5.4. (4S)-4,5-Dihydro-2-(1′-butyl-1′-(2′-pyridinyl)amyl)-4-tert-butyloxazole (**4d**)*

Colorless oil, 81% yield. $[\alpha]_D^{20} = 114$ (c 0.65, EtOH). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.50 (d, $J = 4.6$ Hz, 1H), 7.53 (t, $J = 7.8$ Hz, 1H), 7.28 (d, $J = 7.8$ Hz, 1H), 7.05 (dd, $J = 7.8$ and 4.6 Hz, 1H), 3.97–4.12 (m, 1H), 3.83–3.91 (m, 2H), 1.92–2.01 (m, 4H), 1.09–1.25 (m, 4H), 0.87–1.13 (m, 4H), 0.86 (s, 9H), 0.74–0.81 (m, 6H). IR: 3053w, 2958s, 2870s, 1733w, 1658s, 1260m, 1094s, 1019s. MS: 331 (M^+, 4), 231 (58), 71 (62), 69 (59), 57 (100). HRMS ($C_{21}H_{34}N_2O$): calcd., 330.2671; found, 330.2682.

3. Results and discussion

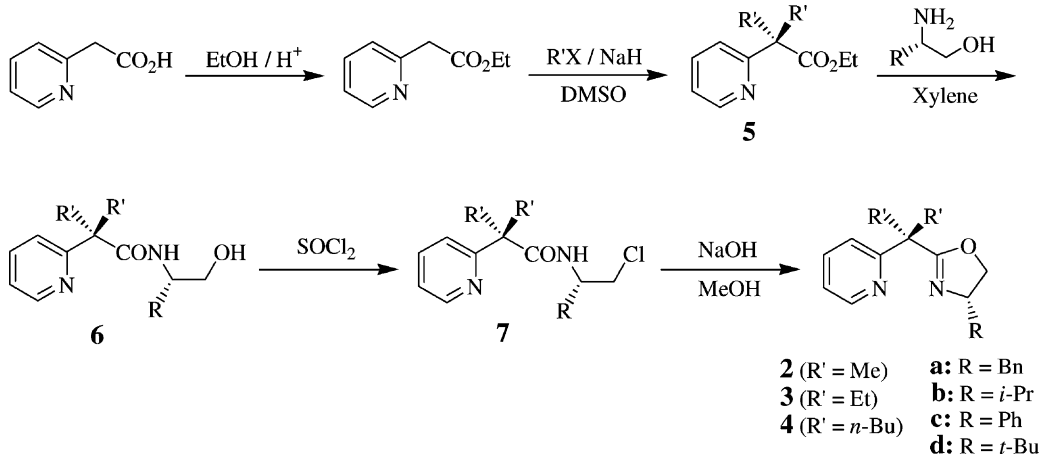
3.1. Synthesis of ligands

Ligands **2**–**4** were synthesized from pyridinylacetic acid and enantiomerically pure amino alcohols using a convenient procedure shown in Scheme 1.[1] Pyridinylacetic acids was converted to its ethyl ester. Alkylations of ethyl pyridinylacetate with alkyl iodides in the presence of NaH in DMSO gave 2,2-disubstituted pyridinylacetates **5** in 72–83% yield. The ester exchange of **5** with optically pure amino alcohols in the refluxing xylene provided amides **6** in 38–62% yield. Conversion of hydroxyl group of the amides **6** with $SOCl_2$ to chlorides **7** in 64–98% yield, followed by cyclization with NaOH in methanol led to formation of the final ligands **2**–**4** in 71–84% yield

3.2. Palladium-catalyzed asymmetric allylic alkylation

To compare the efficiencies of chiral discrimination of ligands **2**–**4** with ligands **1**, asymmetric palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate was performed. The alkylation reaction was carried out in CH_2Cl_2 using chiral catalysts prepared in situ from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and the pyridinyl-oxazoline ligands. The results are summarized in Table 1. Although the time to complete the reactions varied with the ligand used, the yields obtained with ligands **1**–**4** were quite close. It is of significant that ligands **2** gave ee values 17–68% higher than corresponding ligands **1** (Table 1, entries 5–8 versus entries 1–4). Moreover, the enhancement of the enantioselectivities of ligands **2** increased while the substituent on the oxazoline ring changed from benzyl to *t*-butyl. The highest ee (88%) was achieved with ligand **2d**, which was 68% higher than that obtained with ligand **1d** (entry 8 versus entry 4). To extend this enhancement of enantioselectivity, ligands **3** and **4**, with ethyl

[1] Ligands **2** have been reported in our previous paper, see [1b].



Scheme 1.

Table 1
Enantioselective allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate[a]

Entry	Ligand	Time (h)[b]	Yield (%)[c]	ee (%)[d,e]
1	**1a** (R′ = H, R = Bn)	18	90	3
2	**1b** (R′ = H, R = *i*-Pr)	4	83	9
3	**1c** (R′ = H, R = Ph)	75	67	16[f]
4	**1d** (R′ = H, R = *t*-Bu)	138	85	20
5	**2a** (R′ = Me, R = Bn)	28	76	20
6	**2b** (R′ = Me, R = *i*-Pr)	36	93	35
7	**2c** (R′ = Me, R = Ph)	96	92	71
8	**2d** (R′ = Me, R = *t*-Bu)	148	79	88
9	**3b** (R′ = Et, R = *i*-Pr)	48	77	27
10	**3d** (R′ = Et, R = *t*-Bu)	72	81	71
11	**4b** (R′ = *n*-Bu, R = *i*-Pr)	40	79	28
12	**4d** (R′ = *n*-Bu, R = *t*-Bu)	72	82	74

[a] Reaction conditions: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%), ligand (10 mol%), 1,3-diphenyl-2-propenyl acetate (1.0 mmol), BSA (3.6 mmol) and KOAc (3.5 mol%) in dichloromethane (5 ml) at room temperature.

[b] Time for the completion of reactions.

[c] Isolated yields.

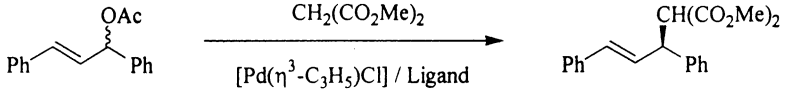
[d] Determined by HPLC with chiral column (DIACEL CHIROCEL OD-H, at 254 nm, *n*-hexane:2-propanol = 99:1, 0.5 ml/min, $t_R = 23.1$ min, $t_S = 24.8$ min).

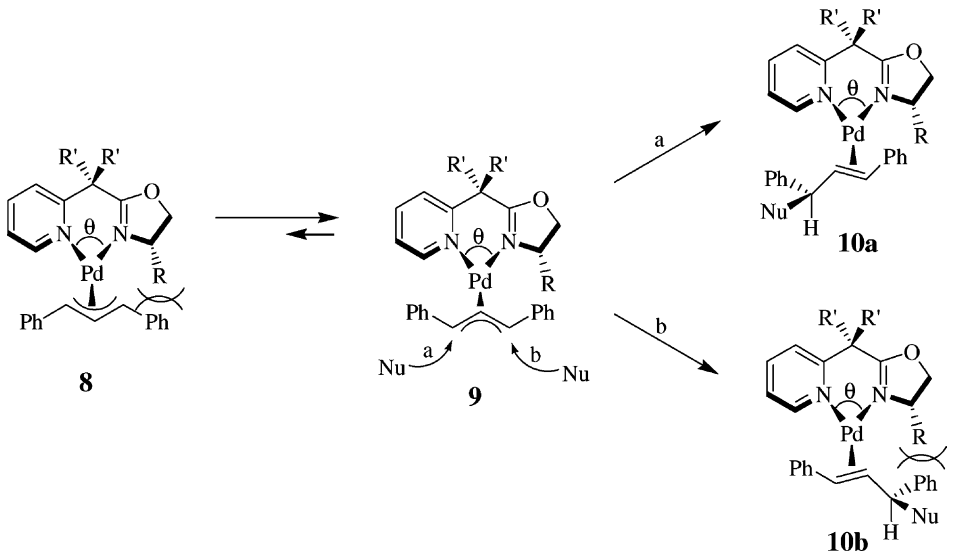
[e] The configuration of product was *S* in all the reactions.

[f] Data taken from [2].

or *n*-butyl on the methylene bridge, were examined in the same condition (entries 9–12). Unfortunately, they provided slightly lower enantioselectivities comparing with ligands **2** (entries 9–12 versus entries 6 and 8).

Mechanistic studies on the palladium-catalyzed allylic alkylation have been well documented [4]. It is generally accepted that, with symmetrically substituted substrates, the enantioselectivity of the reaction is determined by the regioselectivity in the attack of nucleophile to one of two allylic termini in the 1,3-diphenyl-η^3-allylpalladium(II) intermediates [5]. There are a number of possible diastereomeric allylpalladium complexes in the solution which are present at an equilibrium. In the case of palladium catalysts with heteroaryl-oxazoline ligands, the major diastereomeric intermediates are the complexes **8** and **9** with *syn*/*syn* configuration (*endo* and *exo*), which have been demonstrated by NMR in solution [6]. The comparison of steric interactions between the allylic phenyl group and the substitutent on the oxazoline ring in the intermediate palladium complexes showed that the complex **9** is more stable than **8**, and the attack of nucleophile may occur predominantly through the intermediate **9** according to Bosnich's postulation [7].





Scheme 2.

It is assumed nucleophile attacks the terminal allylic carbon *trans* to the oxazoline nitrogen as suggested in the previous studies [2,8], providing the product with *S* configuration which is consistent with experimental result. This selectivity may be explained by a late transition state which related to the steric interactions in the product-like Pd(0)–olefin complex intermediates [4c,5d,9]. It is apparent that the steric interaction between the olefinic phenyl group and the oxazolinic R group in **10a** is smaller than those in **10b**, and the reaction goes favorably through the pathway 'a' in Scheme 2.

Although the simple model provided one of explanations to the enantioselectivity of the reaction, it did not give us much clues to understand how that two substituents on the methylene bridge in ligands **2**–**4**, which are far from the site of reaction, can remarkably enhance the level of chiral discrimination of catalysts. The "substituent effect" in the ligands **2**–**4** might be attributed to the steric repulsion of R′ to two heterocycles, that caused the bite angle (θ) in the allylpalladium intermediates to be smaller and the R group on the oxazoline ring became closer to the reaction site and affects efficiently both the equilibrium and the transition states. This kind of "remote" substituent effect have been known in other asymmetric reactions [10].

4. Conclusions

Because the electronic effect in the heteroaryl-oxazoline ligands is practically negligible, the modifications of this type of ligand to improve the enantioselectivity have been focused on the steric effect. However, the previously reported successful examples involved only the steric interactions which are near to the reaction site [11]. We have shown that the substitution on the remote position can also highly enhance the enantioselectivity of pyridinyl-oxazoline ligands. The finding in this paper provides a new approach for the modification of this kind of ligand.

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