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TETRAHEDRON: *ASYMMETRY*

An efficient phosphorus-containing oxazoline ligand derived from *cis*-2-amino-3,3-dimethyl-1-indanol: application to the palladium-catalyzed asymmetric Heck reaction

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Abstract

Enantiopure 2-[2-(diphenylphosphino)phenyl]oxazoline, derived from a non-natural chiral aminoalcohol, *cis*-2-amino-3,3-dimethyl-1-indanol, was found to be an efficient ligand for the palladium-catalyzed asymmetric Heck reaction.

1. Introduction

In recent years, various types of chiral auxiliaries and catalysts have been developed, enabling the achievement of high enantioselectivities. Until now, most of these were derived from naturally occurring homochiral compounds, and subsequently only one enantiomer can practically be available. In contrast, non-natural chiral auxiliaries are more fascinating from the viewpoint that both enantiomers can be available and their appropriate use in a target asymmetric reaction gives a product with the desired configuration if a method for the resolution of the corresponding racemate is developed.

In the course of our studies concerning resolutions, we have successfully resolved several types of compounds such as amines and aminoalcohols, and applied them to asymmetric reactions.[1–8] Among them, phosphorus-containing oxazoline **2**, derived from *cis*-2-amino-3,3-dimethyl-1-indanol **1**,[9–11] was found to be a more efficient ligand than **3a** and **3b** for a palladium-catalyzed enantioselective allylic amination reaction[12] and a rhodium-catalyzed enantioselective hydrosilylation of ketones.[13]

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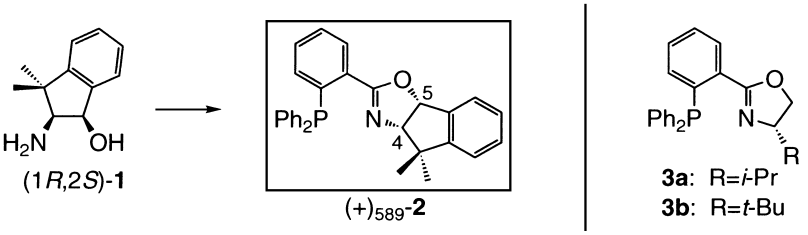
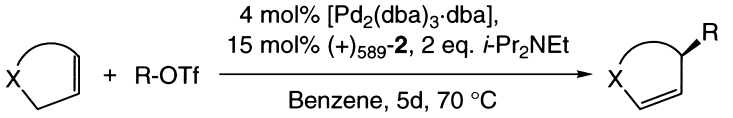
We report herein a successful application of our phosphine-oxazoline ligand **2** in the asymmetric Heck reaction.



Development of the asymmetric Heck reactions, in which a carbon–carbon bond-formation proceeds with high enantioselectivity, would provide a new efficient route to optically active compounds. This methodology was originally developed by Ozawa et al.[14,15] for the reaction of 2,3-dihydrofuran and aryl triflates using a $Pd(OAc)_2$/BINAP catalyst system. Recently, Pfaltz et al. reported that *tert*-leucinol-derived phosphorus-containing oxazoline **3b** was an efficient ligand in the same type of the asymmetric intermolecular Heck reaction.[16,17] Also, Shibasaki et al. and Overman et al. have reported remarkable examples of the more satisfactory enantioselective intramolecular Heck reactions.[18–20] In several cases, chiral phosphinooxazoline ligands gave higher enantiomeric excesses and different product distribution, compared to analogous Pd(BINAP)-catalyzed reactions. Therefore, we tried to use **2** in the intermolecular Heck reaction of cyclic alkenes.

2. Results and discussion

Several reaction conditions were surveyed using a combination of several olefins and phenyl triflate as typical substrates, and the reaction using 4 mol% of $[Pd_2(dba)_3{\cdot}dba]$ and 15 mol% of $(+)_{589}$-**2** with ethyldiisopropylamine in benzene at 70°C was found to be the best. Under these optimized conditions, the asymmetric Heck reactions of aryl and alkenyl triflates were carried out (Scheme 1). The results are summarized in Table 1.

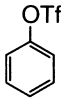
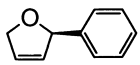
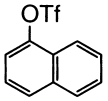
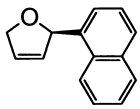
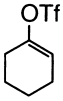
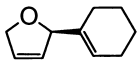
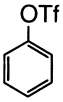
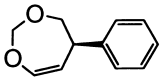


Scheme 1.

As can be seen from Table 1, good to excellent enantioselectivities were achieved in all cases. In particular, the reaction of 1-cyclohexenyl triflate with 2,3-dihydrofuran (entry 3) proceeded smoothly even at rt to give a satisfactory result. In contrast, the size of the alkenes dramatically influenced the yield (entry 4), although the enantioselectivity was maintained. These results indicate that the conformationally fixed two methyl groups of $(+)_{589}$-**2** effectively induces chirality to the products, and that the rigidity of the methyl groups probably disturbs bulky alkenes, such as 4,7-dihydro-1,3-dioxepin, to coordinate to the metal.

The absolute configurations of the products, produced by using $(+)_{589}$-**2**, are all *R*, whereas the absolute configuration of the 4-position of the oxazoline moiety in $(+)_{589}$-**2** is *S*. This result is consistent with those obtained by using other phosphorus-containing oxazolines, meaning that

Table 1
The asymmetric Heck reaction using chiral ligand $(+)_{589}$-**2**[a]

entry	olefin	R-OTf	product	yield/%	% e.e. (config.)
1				81	96[b] (*R*)
2				64	94[b] (*R*)
3[c]				91	98[d] (*R*)
4				37	90[b] (*R*)

[a]The absolute configuration of the products was deduced by comparison of the sign of its specific rotation with that in the literature.[17] [b]Determined by chiral HPLC analysis (Daicel Chiralcel OD). [c]The reaction was carried out at r.t. [d]Determined by Chiral GC analysis (*Chiraldex* γ-CD-TFA) .

the absolute configuration of the products of the present reaction is controlled by the absolute configuration of the 4-position of **2**. This ligand also had a low tendency to promote a carbon–carbon double bond migration, which was the same as the other phosphinooxazoline ligands. In contrast to the fact that a mixture of 2,3- and 2,5-dihydro-2-phenylfurans was obtained from the same substrate as in entry 1, when BINAP was used as the ligand,[14] no migration of the carbon–carbon double bond was observed by using **2**; only 2,5-dihydro-2-phenylfuran was formed.

3. Conclusion

We have successfully applied 2-[2-(diphenylphosphino)phenyl]oxazoline **2**, derived from an artificial chiral aminoalcohol **1**, to the palladium-catalyzed asymmetric Heck reaction. It is noteworthy that both enantiomers of this ligand are readily available from both enantiomers of **1**, respectively, which were obtained by resolution. Thus, **2** was found to be an efficient ligand for the palladium-catalyzed asymmetric Heck reaction.

4. Experimental

4.1. General

The starting materials and reagents, purchased from commercial suppliers, were used after standard purification. *cis*-2-Amino-3,3-dimethyl-1-indanol was synthesized and resolved according

to the procedure previously reported by us.[9] Solvents were dried over sodium wire or molecular sieves, and were distilled before use. Reaction flasks were flame-dried under a stream of Ar. All moisture- and oxygen-sensitive reactions were conducted under an Ar atmosphere. Flash chromatography was carried out using silica gel 60 (70–230 mesh). Preparative TLC (PTLC) was carried out with Wakogel B-5F. 'Usual workup' represents the sequence of drying the combined extracts over Na_2SO_4, filtering off Na_2SO_4, and concentrating the filtrate under reduced pressure.

The melting points are uncorrected. HPLC analysis was performed with detection by UV light. ^{1}H NMR (300 MHz) spectra were measured in $CDCl_3$ with Me_4Si as an internal standard; the δ and J values are given in parts per million and hertz, respectively. IR spectral data is recorded in units of cm^{-1}.

*4.2. (*3aR,8bS*)-2-[2-(Diphenylphosphino)phenyl)-3a,8b-dihydro-4,4-dimethyl-4*H*-indeno[1,2-*d*]-oxazole ((+)$_{589}$-**2**)*

Compound **2** was synthesized from (1*R*,2*S*)-2-amino-3,3-dimethyl-1-indanol according to our previous report[12] with slight modification described as follows.

*4.2.1. (3a*R*,8b*S*)-2-(2-Fluorophenyl)-3a,8b-dihydro-4,4-dimethyl-4*H*-indeno[1,2-*d*]oxazole*

To a suspension of $ZnCl_2$ (35 mg) and (1*R*,2*S*)-2-amino-3,3-dimethyl-1-indanol (538 mg, 3.04 mmol) in chlorobenzene (7 mL) was added 2-fluorobenzonitrile (0.44 g, 3.6 mmol), and the mixture was stirred for 60 h under reflux. An interrupting reflux caused a decrease in the yield of the product. After the mixture was concentrated under reduced pressure, purification by column chromatography (hexane:ethyl acetate, 19:1) gave the title compound as a greenish amorphous mass (711 mg, 2.53 mmol, 83%), which was used for the following reaction without further purification.

*4.2.2. (3a*R*,8b*S*)-2-[2-(Diphenylphosphino)phenyl)-3a,8b-dihydro-4,4-dimethyl-4*H*-indeno[1,2-*d*]-oxazole ((+)$_{589}$-**2**)*

To potassium diphenylphosphide[21] (34 mL, 9.2 mmol; 0.27 M solution in THF:dioxane, 4:6) was added a solution of (3a*R*,8b*S*)-2-(2-fluorophenyl)-3a,8b-dihydro-4,4-dimethyl-4*H*-indeno[1,2-*d*]-oxazole (1.30 g, 4.62 mmol) in THF (5 mL) at 0°C, and the resulting solution was stirred for 1 h at rt. The reaction was quenched by adding water (30 mL), and the mixture was extracted with ether (3×20 mL). After usual workup, purification by column chromatography (hexane:ethyl acetate, 19:1) gave (+)$_{589}$-**2** as a colorless amorphous mass (1.43 g, 3.19 mmol, 65%).

*4.3. General procedure for the asymmetric Heck reaction using (+)$_{589}$-**2** as a ligand*

To a mixture of [Pd_2(dba)$_3$·dba] (23 mg, 20 μmol) and (+)$_{589}$-**2** (36 mg, 80 μmol) in Ar-saturated benzene (3 mL), which had been pre-stirred at rt for 10 min, was added an aryl or alkenyl triflate (0.5 mmol). Then an alkene (2 mmol) and ethyldiisopropylamine (1 mmol) were successively added, and the resultant solution was stirred at 70°C or rt for 5 days. The mixture was diluted with hexane (ca. 50 mL) to quench the reaction. The resulting orange suspension was filtered through a 2 cm layer of silica gel, and the silica gel was washed upon eluting Et_2O. The concentration of the combined filtrate and eluate gave a yellow oil, which was purified by column chromatography to afford the product. All of the products described here were identified by comparison of the ^{1}H NMR spectra and GC/HPLC analysis with those in the literature.[17]

*4.3.1. (*R*)-2-Phenyl-2,5-dihydrofuran*

The title compound was obtained from phenyl triflate (114 mg, 0.5 mmol) and 2,3-dihydrofuran (145 mg, 2.0 mmol) in an 81% isolated yield. ^{1}H NMR 4.76 (dddd, J = 1.5, 2.4, 4.2, 12.6 Hz, 1H), 4.88 (dddd, J = 1.5, 2.4, 6.0, 12.6 Hz, 1H), 5.80 (dddd, J = 1.8, 3.9, 6.0, 7.8 Hz, 1H), 5.89 (dtd, J = 1.5, 2.4, 6.0 Hz, 1H), 6.04 (ddt, J = 1.5, 2.4, 6.0 Hz, 1H), 7.25–7.40 (m, 5H). The absolute configuration was determined as *R* by comparison of its specific rotation with that in the literature;[17] $[\alpha]_D$ = +282 (c = 0.92, $CHCl_3$, 18°C). The enantiomeric excess was determined as 96% by an HPLC analysis using chiral column: Daicel Chiralcel OD, hexane, 1 mL/min, 35.5 min (+), 42.6 min (–).

*4.3.2. (*R*)-2-(1-Naphthyl)-2,5-dihydrofuran*

The title compound was obtained from 1-naphthyl triflate (142 mg, 0.5 mmol) and 2,3-dihydrofuran (140 mg, 2.0 mmol) in 64% isolated yield. ^{1}H NMR 4.84–4.99 (m, 2H), 6.07–6.17 (m, 2H), 6.55–6.59 (m, 1H), 7.43–7.57 (m, 4 H), 7.78–7.89 (m, 2H), 8.12–8.15 (m, 1H). The enantiomeric excess was determined as 94% by an HPLC analysis using chiral column: Daicel Chiralcel OD, hexane:2-propanol = 9:1, 0.5 mL/min, 16.8 min (+), 19.9 min (–).

*4.3.3. (*R*)-2-(1-Cyclohexen-1′yl)-2,5-dihydrofuran*

The title compound was obtained from 1-cyclohexenyl triflate (120 mg, 0.52 mmol) and 2,3-dihydrofuran (140 mg, 2.0 mmol) at rt in 81% isolated yield. ^{1}H NMR 1.44–1.73 (m, 4H), 1.78–2.20 (m, 4H), 4.63 (dddd, J = 1.8, 2.7, 4.2, 12.6 Hz, 1H), 4.69 (dddd, J = 1.5, 2.4, 5.7, 12.6 Hz, 1H), 5.10–5.16 (m, 1H), 5.68–5.72 (m, 2H), 5.95 (ddt, J = 1.5, 2.4, 6.3 Hz, 1H). The enantiomeric excess was determined as 98% by a GC analysis using chiral column: Chiraldex γ-CD-TFA, 120kpa, 80–120°C, 0.3°C/min, 22.0 min (–), 23.3 min (+).

*4.3.4. (*R*)-4,5-Dihydro-5-phenyl-1,3-dioxepin*

The title compound was obtained from phenyl triflate (179 mg, 0.79 mmol) and 4,7-dihydro-1,3-dioxepin (319 mg, 3.18 mmol) in 37% isolated yield. ^{1}H NMR 3.46 (dd, J = 8.7, 11.7 Hz, 1H), 3.77–3.84 (m, 1H), 3.98 (ddd, J = 0.6, 4.8, 11.7 Hz, 1H), 4.85 (d, J = 6.9 Hz, 1H), 4.94 (ddd, J = 0.6, 3.9, 7.2 Hz, 1H), 5.19 (d, J = 6.9 Hz, 1H), 6.47 (dd, J = 2.4, 7.2, 1H), 7.20–7.40 (m, 5 H). The enantiomeric excess was determined as 90% by an HPLC analysis using chiral column: Daicel Chiralcel OD, hexane:2-propanol = 99:1, 0.5 mL/min, 12.1 min (+), 14.4 min (–).

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