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Readily available phosphine–imine ligands from α-phenylethylamine for highly efficient Pd-catalyzed asymmetric allylic alkylation

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Abstract

A series of novel chiral phosphine–imine ligands have been prepared by a two-step transformation from chiral α-phenylethylamine. The resulting chiral ligands were found to be effective for the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-en-1-yl pivalate with dimethyl malonate, in which up to 94% ee and 99% conversions were obtained. The results demonstrate that the chirality resided on the chelate ring of P–Pd–N complex is more effective for the transfer of the stereochemical information by comparison with the result obtained by Hashimoto and coworkers' phosphine–imine ligand, in which the chirality lay in the outside of P–Pd–N chelate ring. The effect of solvent, base and substitutent in phosphine–imine ligand on this catalytic reaction is also described.

Keywords: Palladium; Phenylethylamine; Phosphine–imine ligand; Asymmetric; Allylic alkylation

1. Introduction

The asymmetric alkylation of allylic electrophiles catalyzed by palladium complexes has been extensively investigated due to the synthetic potential of the products of these types of reactions [1–3]. A wide variety of ligands have been found to be effective for these transformations. Among them, chiral phosphine–Schiff-based imine ligands have received increasing attention recently due to their flexible coordination behaviors associated with tunable steric and electronic properties [4–14]. By appropriately electronic and steric modification, many phosphine–imine ligands have been developed and shown to be very effective in the Pd-catalyzed asymmetric allylic substitution. Recently, Hashimoto and coworkers reported a series of phosphine–imine ligands **1** derived from 1-arylethylamines and 2-(diphenylphosphino)benzaldehyde and examined their enantioselective induction in Pd-catalyzed asymmetric allylic alkylation [15]. It's found that most of these phosphine–imine ligands showed poor enantioselectivity, and good enantioselectivity could be obtained only when sterically congested (*R*)-1-mesitylethylamine was used as the amine component. This is perhaps not surprising, as these phosphine–imines were derived from 2-(diphenylphosphino)benzaldehyde, with the chirality remote from the reaction center, residing on the conformationally labile amino portion of the imine. We then surmised that if the chirality was placed on the chelate ring of P–Pd–N complex, the transfer of the stereochemical information might be more efficient. A new class of phosphine–imine ligands **2** are then proposed, which seemed ideal species to investigate since the Pd-complex formed by the reaction of these ligands with Pd precursor possess the chirality held in fairly rigid conformations. Our interest was augmented by our ready access to a chiral amino-phosphine precursor, (*S*)-1-[2-(diphenylphosphino)phenyl]ethylamine [(*S*)-DPPNH$_2$, **3**], easily prepared from commercially available, inexpensive chiral 1-phenylethylamine, which are the final intermediates in the synthesis of a variety of recently introduced phosphine–phosphoramidite ligands (PEAPhos) for highly efficient Rh-catalyzed asymmetric hydrogenation [16]. As a result, herein we report our results in the development of this kind of phosphine–imine ligands for highly efficient Pd-catalyzed asym-

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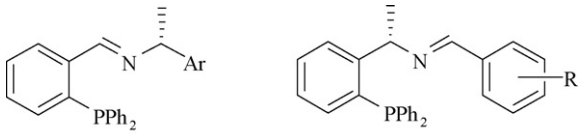

1a : Ar = Ph; **1b** : Ar = mesityl

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Fig. 1. The structures of phosphine–imine ligands **1** and **2**.

metric allylic alkylation, in which up to 94% ee was obtained (Fig. 1).

2. Experimental

2.1. General methods

Melting points were measured on a Yazawa micro melting point apparatus (uncorrected). Optical rotations were measured on a JASCO P-1020 high sensitive polarimeter. The ^{1}H NMR spectra were recorded on a BRUKER DRX 400 system with TMS as an internal standard. The ^{31}P NMR spectra were recorded using a BRUKER DRX 400 system with 85% phosphoric acid as the external standard. Enantiomeric excesses (% ee) were determined by HPLC analysis using a Chiralpak AD column. All experiments were carried out under an argon atmosphere using standard Schlenk techniques. All solvents were dried using standard procedures. 1,3-Diphenylprop-2-en-1-yl pivalate **7** was prepared following a modified method for the corresponding acetate analogue [17]. All other chemicals were obtained commercially.

2.2. Synthesis of (S)-1-[2-(diphenylphosphino)phenyl] ethylamine [(S)-DPPNH$_2$] (**3**)

To a solution of (*S*)-1-phenylethylamine **4** (1.21 g, 10.0 mmol) in 10 ml of ether at −35 °C was added 6.25 ml (10.0 mmol) of a 1.6 M solution of *n*-BuLi in hexane dropwise. The resulting solution was stirred at −35 °C for 30 min, and then 1.39 ml (11.0 mmol, 1.1 equiv.) of Me_3SiCl was added slowly at the same temperature. The reaction mixture was stirred for another 2 h. Then 18.8 ml (30.0 mmol, 3.0 equiv.) of a 1.6 M solution of *n*-BuLi was added dropwise and the reaction mixture was allowed to slowly warm to room temperature during 5 h and stirred overnight. The reaction mixture was cooled to −35 °C, and a solution of 1.80 ml (10.0 mmol) of chlorodiphenylphosphine in 10 ml of ether was added dropwise during 1 h. The reaction mixture was stirred for another 3 h at the same temperature, and then warmed to room temperature. After stirring for another 4 h, a solution of 1.0 M aqueous HCl was added slowly until the reaction mixture became clear in both phases. The aqueous phase was extracted with ether (3 × 10 ml). Combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/acetate, 8/1) to give 1.22 g (40% yield) of the targeted (*S*)-DPPNH$_2$ **3** as a white solid; mp 80–82 °C; $[\alpha]_D^{13}$ 56.7 (c 0.53, $CHCl_3$); ^{1}H NMR (DMSO-d^6) δ 1.23 (d, J = 6.8 Hz, 3H), 1.38 (s, 2H), 4.90 (m, 1H), 6.83–7.59 (m, 14H); ^{31}P NMR (DMSO-d^6) δ −16.3; HRMS (APCI) calcd. for $C_{20}H_{20}NP$ (M + 1) 306.1406, found 306.1376.

2.3. General procedure for the synthesis of phosphine–imine ligands (**2**)

To a solution of (*S*)-DPPNH$_2$ **3** (305 mg, 1.0 mmol) in 5.0 ml of ethanol was added the corresponding benzaldehyde (1.0 mmol) and anhydrous $MgSO_4$ (600 mg). The reaction mixture was heated to reflux. After the reaction was complete (detected by TLC), the reaction mixture was diluted with CH_2Cl_2. $MgSO_4$ was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography.

2.3.1. (S)-N-(3-Nitrobenzylidene)-1-[2-(diphenylphosphino)phenyl]ethylamine (**2a**)

Green crystal; 62% yield; mp 99–101 °C; $[\alpha]_D^{14}$ 48.8 (c 1.10, $CHCl_3$); ^{1}H NMR (DMSO-d^6) δ 1.38 (d, J = 6.4 Hz, 3H), 5.40 (m, 1H), 6.76–8.28 (m, 18H), 8.38 (s, 1H); ^{31}P NMR (DMSO-d^6) δ −17.6; HRMS (APCI) calcd. for $C_{27}H_{23}N_2O_2P$ (M + 1) 439.1569, found 439.1554.

2.3.2. (S)-N-(3-Trifluoromethylbenzylidene)-1-[2-(diphenylphosphino)phenyl]ethyl-amine (**2b**)

White solid; 34% yield; mp 85–87 °C; $[\alpha]_D^{14}$ 34.2 (c 1.01, $CHCl_3$); ^{1}H NMR (DMSO-d^6) δ 1.46 (d, J = 6.4 Hz, 3H), 5.47 (m, 1H), 6.85–7.99 (m, 18H), 8.22 (s, 1H); ^{31}P NMR (DMSO-d^6) δ −17.6; HRMS (APCI) calcd. for $C_{28}H_{23}F_3NP$ (M + 1) 462.1593, found 462.1610.

2.3.3. (S)-N-(3-Methoxybenzylidene)-1-[2-(diphenylphosphino)phenyl]ethylamine (**2c**)

White solid; 54% yield; mp 110–112 °C; $[\alpha]_D^{14}$ 62.9 (c 0.98, $CHCl_3$); ^{1}H NMR (DMSO-d^6) δ 1.32 (d, J = 6.4 Hz, 3H), 3.77 (s, 3H), 5.29 (m, 1H), 6.99–7.79 (m, 18H), 7.96 (s, 1H); ^{31}P NMR (DMSO-d^6) δ −17.5; HRMS (APCI) calcd. for $C_{28}H_{26}NOP$ (M + 1) 424.1824, found 424.1813.

2.3.4. (S)-N-(2-Methoxybenzylidene)-1-[2-(diphenylphosphino)phenyl]ethylamine (**2d**)

White crystal; 43% yield; mp 140–142 °C; $[\alpha]_D^{14}$ −15.1 (c 0.66, $CHCl_3$); ^{1}H NMR (DMSO-d^6) δ 1.31 (d, J = 6.4 Hz, 3H), 3.80 (s, 3H), 5.26 (m, 1H), 6.94–7.80 (m, 18H), 8.39 (s, 1H); ^{31}P NMR (DMSO-d^6) δ −17.4; HRMS (APCI) calcd. for $C_{28}H_{26}NOP$ (M + 1) 424.1824, found 424.1798.

2.3.5. (S)-N-(2-Chlorobenzylidene)-1-[2-(diphenylphosphino)phenyl]ethylamine (**2e**)

White crystal; 58% yield; mp 88–90 °C; $[\alpha]_D^{14}$ −34.8 (c 0.8, $CHCl_3$); ^{1}H NMR (DMSO-d^6) δ 1.31 (d, J = 6.4 Hz, 3H), 5.36 (m, 1H), 6.77–7.89 (m, 18H), 8.38 (s, 1H); ^{31}P NMR (DMSO-d^6) δ −17.1; HRMS (APCI) calcd. for $C_{27}H_{23}NPCl$ 427.1257, found 427.1253.