Synthesis of chiral P,N-ligands derived from quinoline and their application in asymmetric allylic alkylations

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Chiral P,N-ligands derived from quinoline and with a *trans* and *cis* cyclohexane backbone were easily synthesised in four steps from quinoline N-oxide. The enantiopure *trans* isomer was obtained by the way of chiral resolution of the mixture of *trans*- and *cis*-2-(quinolin-2-yl)cyclohexanol with dibenzoyltartaric acid and then subjected to a Mitsunobu reaction and deprotection to give the corresponding *cis* isomer. The optical pure *trans* and *cis* isomer reacted with chlorodiphenylphosphine or PAr_2NEt_2 to obtain *trans* and *cis* P,N-ligands, which were used in asymmetric allylic alkylations with up to 78% ee and 84% ee respectively.

Key words: P,N-ligands, quinoline, chiral resolution, allylic alkylations

Asymmetric transformations in the presence of chiral ligands have proved to be one of the most efficient methods for the construction of enantioenriched chiral compounds.[1] The development of phosphorus- and nitrogen-based chiral ligands has been extensively investigated in late-transition-metal catalysis.[2–4] Zhou and Pfaltz have successfully used chiral P,N-ligands with a cyclohexane-backbone and bicyclic P,N-ligands in the Pd-catalysed allylic alkylations.[5,6] However, P,N-ligands derived from quinoline have been reported in only a few examples. In the present work, we describe the synthesis of chiral P,N-ligands derived from quinoline and their application in asymmetric allylic alkylations.

Following literature precedents,[7–10] the reaction of quinoline N-oxide with the enamine of cyclohexanone in the presence of an acylating agent gave ketone **3**. This was treated with $NaHB_4$ in 95% ethanol for 10 min at room temperature to give a nearly quantitative yield of a mixture of the *trans* and *cis* alcohols **4** and **5**. The stereochemistry of the two isomers was established from their ^{1}H NMR spectra. The chemical shift of the major isomers (*trans* OH) was larger than that of the minor isomers (*cis* OH), which indicates the presence of an intramolecular hydrogen bonding in **5**.[10,11] The ratio of *trans* and *cis* isomers was 71:29. The *cis* and *trans* isomers could be easily separated by column chromatography.

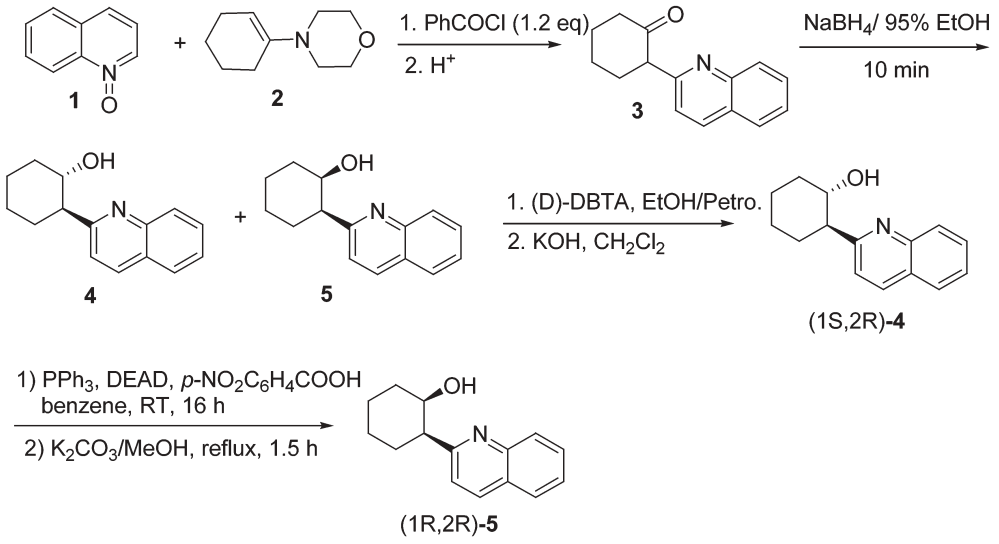
The optical resolution of the isomers was then carried out. Kita *et al*. reported kinetic resolution of (±)-*trans*-2-pyridylcyclohexanols using chiral 3β-acetoxyetienic acid, DCC and DMAP[12,13]. Zhou reported a convenient method to obtain enantiopure *trans*- and *cis*-pyridyl cyclohexanols with inexpensive tartaric acid derivatives.[6] Here, we found the dibenzoyl tartaric acid (DBTA) was an efficient resolving agent. (D)-DBTA in a mixture of solvents was used to resolve the racemic *trans* and *cis* mixtures. The crude diastereomeric salt was then recrystallised three times to obtain (1S,2R)-**4** in 22% yield and more than 99%ee. Then, the *trans* isomer (1S, 2R)-**4** was transformed to the *cis* isomer (1R, 2R)-**5** by a Mitsunobu reaction.[6,14] Reaction of *trans*-**4** with BuLi and PPh_2Cl in THF gave *trans*-ligand **6**, and using Pfaltz's condition, reaction of *cis*-**5** with PAr_2NEt_2/4,5-dichloroimidazole/Et_3N (1:1:1, 1.5 equiv) under reflux gave the desired *cis*-ligand **7**.[5]

Finally, we examined the palladium-catalysed asymmetric allylic alkylation of racemic 1,3-diphenyl-2-propenyl acetate (**8**) with 3.0 equiv. of dimethyl malonate (DMM) using chiral P,N-ligand **6** or **7** in CH_2Cl_2 for 2 h at 25 °C.

For ligand **6**, the reaction proceeded in 96% conversion and enantiomeric excess of up to 78%; for ligand **7**, the reaction proceeded in 95% conversion and enantiomeric excess of up to 84%.

Experimental

Solvents and reagents were obtained from commercial sources and used without further purification. Melting points were determined on a Mettler FP5 melting point apparatus and are uncorrected. NMR spectra were recorded on Bruker DRX 400 MHz spectrometer using DMSO-*d*6, $CDCl_3$ as solvent, and tetramethylsilane (TMS) as internal standard. Optical rotations were measured with a JASCO P-1020



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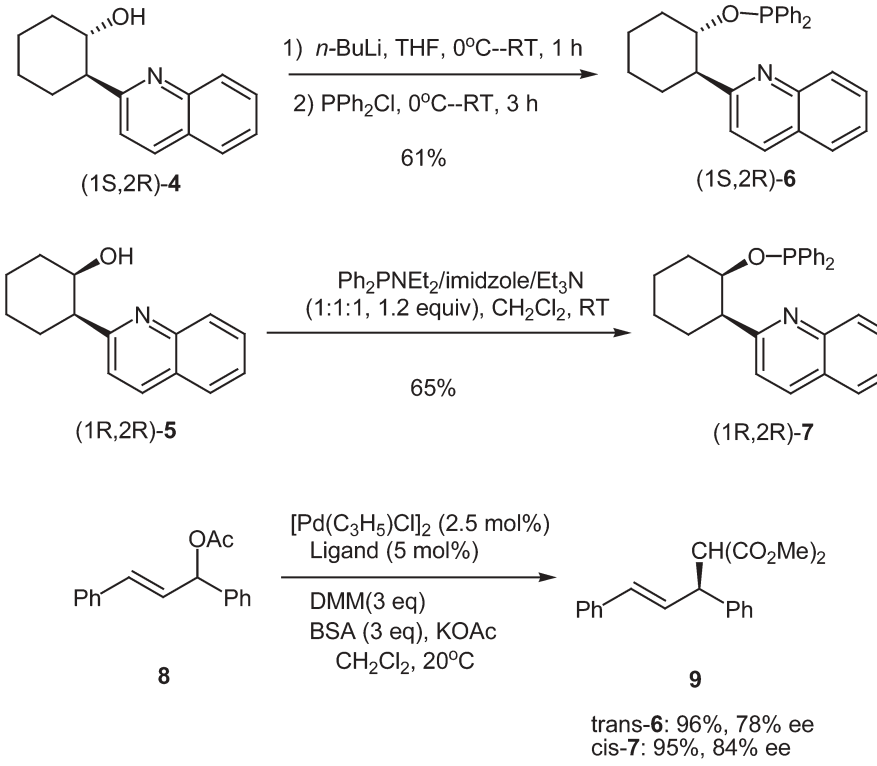

automatic polarimeter. High resolution mass spectra were recorded on Applied Biosystems Mariner System 5303. Enantiomeric excess (e.e.) determination was carried out using HPLC with a Chiralcel AS-H and AD-H column on an Agilent 1100 Series HPLC instrument.

The reduction of ketone: $NaBH_4$ (0.418 g, 11 mmol) was added to a solution of ketone **3** (2.25 g, 10 mmol) in EtOH (50 mL) at 0 °C, and the mixture was stirred for 0.5h at room temperature. Then, the solvent was removed under vacuum. Water was added to the residue and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4 and evaporated in vacuum to give the product (*cis* and *trans*) as a diastereomeric mixture. The *cis* and *trans* isomers could be easily separated by column chromatography and their structure was confirmed by NMR.

(±)-trans-*2-Quinolin-2ylcyclohexanol* **(4)**: [10] M.p. 129–131 °C (lit.[10]:129–130 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ8.10 (d, *J* = 8.6 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.68 (td, *J* = 7.6, 1.2 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 4.58 (br, 1H), 4.15 (td, *J* = 10.0, 4.1 Hz, 1H), 2.86 (td, *J* = 10.6, 3.0 Hz, 1H), 2.16–2.19 (m, 2H), 1.84–1.86 (m, 2H), 1.44–1.54 (m, 4H).

(±)-cis-*2-Quinolin-2ylcyclohexanol* **(5)**:[11] M.p.123–124 °C (lit.[11]: 126 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ8.10 (d, *J* = 8.3 Hz, 1 H), 8.01 (d, *J* = 8.3 Hz, 1 H), 7.78 (d, *J* = 7.9 Hz, 1 H), 7.69 (t, *J* = 8.3 Hz, 1 H), 7.51 (t, *J* = 8.0 Hz, 1 H), 7.27 (d, *J* = 8.3 Hz, 1 H), 6.53 (*br*s, 1 H), 4.45 (s, 1 H), 2.88–2.92 (m, 1 H), 2.03–2.09 (m, 2 H), 1.84–1.87 (m, 2 H), 1.63–1.73 (m, 2 H), 1.45–1.55 (m, 2 H).

Resolution of 2-(quinolin-2-yl)cyclohexanol with DBTA: DBTA (25.6 g, 71.5 mmol) was added to compound **4** (16.2 g, 71.4 mmol) in a mixed solvent (250 mL ethanol and 250 mL petroleum ether) at 0 °C, and the reaction mixture was heated for several minutes until it became clear. Then it was allowed to room temperature and kept stirring overnight. A white solid precipitated and was collected by filtration and washed with a small amount of petroleum ether (30 mL). The solid was crystallised a second time by adding 350 mL of ethanol and 150 mL of petroleum ether and then heating to reflux and cooling to room temperature. The process was repeated three more times with 280 mL and 200 mL, 180 mL and 100 mL, 130 mL and 100 mL of ethanol and petroleum ether (all wash with 10 mL of petroleum ether) respectively. After drying *in vacuo* for 2h, the final diastereomeric salt precipitated and filtered as a white solid (3.2 g). It was dissolved in CH_2Cl_2 (25ml) and 1M KOH(10 ml). The mixture was stirred for 30 min, and the organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuum to give (1S,2R)-**4** as white solid.

(1S,2R)-trans-*2-(quinolin-2-yl)cyclohexanol* **(4)**: M.p. 155°C. $[\alpha]^{27}_D$ = –23.7 (*c* 0.42, $CHCl_3$); >99% ee. (Chiralcel AS-H column, *i*-PrOH/hexane 10/90, 1.0 mL min^{-1}, 254nm: $t_{(1S,\,2R)}$ = 7.2 min, $t_{(1R,\,2S)}$ = 9.1 min)].

(1R,2R)-cis-*2-(quinolin-2-yl)cyclohexanol* **(5)**: A solution of DEAD (3.0 mmol) in benzene (20 mL) was slowly added under a N_2 atmosphere to the mixture of (1S,2R)-*trans*-2-(quinolin-2-yl)cyclohexanol (**4**) (454mg, 2.0 mmol), *p*-$NO_2C_6H_4COOH$ (502 mg, 3.0 mmol) and PPh_3 (786 mg, 3.0 mmol) in 30 mL benzene at 0 °C. The mixture was stirred at room temperature for 24h. The solvent was removed under reduced pressure and the residue was immediately subjected to flash chromatography to give (1R,2R)-*cis*-2-(quinolin2-yl)cyclohexyl-4-nitrobenzoate. The resulting carboxylic esters were dissolved in MeOH (20 mL) and K_2CO_3 (1.38 g, 10 mmol) was added. The solution was stirred under reflux for 3 h. The reaction mixture was concentrated *in vacuo* to dryness and then diluted with water (120 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was successively washed with KOH (1N), H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the white crystalline solid (1R,2R)-*cis*-2-(quinolin-2-yl)cyclohexanol **5** in 91% yield. M.p.150–152 °C $[\alpha]^{26}_D$ = +19.3 (*c* 0.78, $CHCl_3$).

[(1S,2R)-trans-*2-Quinolin-2ylcyclohexan-1-oxy]diphenyl phosphine* **(6)**: *n*-BuLi (2.5 M in hexane, 0.52 mL) was added to a Schlenk flask containing (1S,2R)-*trans*-2-(quinolin-2-yl)cyclohexanol **4** (297 mg, 1.31 mmol) in THF (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was then cooled to 0 °C and chlorodiphenylphosphine (0.27 mL, 1.44 mmol) was added using a syringe. The reaction mixture was again allowed to warm to room temperature and stirred for 3 h. The solvent was removed *in vacuo*, and the reaction was diluted with 95:5 hexane-AcOEt (1.5 mL). The resulting slurry was loaded onto a plug of silica and purified by flash chromatography (hexane/AcOEt = 95:5) to yield **6** as a pale yellow oil.

[(1S,2R)-trans-*2-Quinolin-2ylcyclohexan-1-oxy]diphenyl phosphine* **(6)**: $[\alpha]^{26}_D$ = +26.1 (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ8.16 (d, *J* = 8.4 Hz, 1 H), 7.88–7.91 (m, 2 H), 6.70 (m, 1 H), 7.54 (t, *J* = 7.9 Hz, 1 H), 7.47 (d, *J* = 8.4 Hz, 1 H), 7.29–7.31 (m, 5 H), 6.89 (t, *J* = 7.9 Hz, 1 H), 6.66 (t, *J* = 7.7 Hz, 1 H), 6.50 (t, *J* = 7.5 Hz, 1 H), 4.39–4.44 (m, 1 H), 3.10–3.16 (m, 1 H), 2.16–2.19 (m, 1 H), 1.69–1.92 (m, 3 H), 1.35–1.52 (m, 4 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ24.4, 25.0, 32.1, 34.3, 53.9 (d, *J* = 6.2 Hz), 82.5 (d, *J* = 20.1 Hz), 121.7, 125.6, 126.9, 127.2, 127.3, 127.6, 128.1, 128.2, 128.5, 128.6, 128.8, 129.0, 129.1, 129.4, 129.7, 136.1, 141.7 (d), 143.0 (d, *J* = 17.1

Hz), 147.4, 163.6; ^{31}P NMR (162 MHz, DMSO-d_6): δ105.8; HRMS Calcd for $C_{27}H_{27}NOP$ (M+1) 412.183. Found: 412.184.

[(1R,2R)-cis-*2-Quinolin-2ylcyclohexan- 1-oxy]diphenyl phosphine* (**7**): (1R,2R)-*cis*-2-(quinolin-2-yl)cyclohexanol **5** (68 mg, 0.30 mmol), 4,5-dichloro imidazole (62 mg, 0.45 mmol) were dissolved in CH_2Cl_2 (4 mL) to give a white suspension. Triethylamine (63 µl, 0.45 mmol) was added to the reaction mixture to give a clear solution. The mixture was cooled to 0 °C and *N*-ethyl-*N*-(diphenylphosphino)ethanamine (116 mg, 0.45 mmol) dissolved in CH_2Cl_2 (2 mL) was added. The cooling bath was removed and the solution was heated to reflux for 6 h until the reaction was complete (TLC). The mixture was then concentrated and directly purified by flash chromatography (hexane/EtOAc = 10:1–15:1) to yield **7** as a white solid (80 mg, 65%).

[(1R,2R)-cis-*2-Quinolin-2ylcyclohexan-1-oxy]diphenyl phosphine* (**7**): M.p. 70–72 °C, $[\alpha]^{25}_D$ = –265.5 (*c* 1.34, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ8.15 (d, *J* = 8.6 Hz, 1 H), 7.91 (t, *J* = 8.1 Hz, 2 H), 7.71 (m, 1 H), 7.55 (t, *J* = 7.0 Hz, 1 H), 7.48 (d, *J* = 8.6 Hz, 1 H), 7.32–7.40 (m, 5 H), 6.94 (m, 1 H), 6.58–6.68 (m, 4 H), 4.62–4.64 (m, 1 H), 3.20 (m, 1 H), 2.36–2.39 (m, 1 H), 2.04–2.07 (m, 1 H), 1.90–1.98 (m, 2 H), 1.73 (m, 1 H), 1.48–1.53 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ19.6, 23.8, 25.1, 31.5, 49.2 (d, *J* = 5.7 Hz), 79.0 (d, *J* = 19.8 Hz), 120.6, 125.7, 126.7, 127.4, 127.5, 127.6, 127.8, 128.3, 128.4, 128.5, 128.7, 128.9, 129.2, 129.6, 129.8, 130.8, 135.8, 141.9 (d), 143.2 (d), 147.1, 162.9; ^{31}P NMR (162 MHz, DMSO-d_6): δ104.1; HRMS Calcd for $C_{27}H_{27}NOP$ (M+1) 412.18248. Found: 412.18309.

Allylic alkylations with dimethyl malonate: CH_2Cl_2 (1mL) followed by $[(C_3H_5)PdCl]_2$ (2.3 mg, 0.0063 mmol) was added to a Schlenk flask containing ligand **6** or **7** (5.1mg, 0.0125 mmol). The mixture was stirred at room temperature for 1 h. Potassium acetate (1.2 mg) and the allylic acetate (63 mg, 0.25 mmol) dissolved in 1 mL CH_2Cl_2 was added to the reaction and the reaction solution was stirred at room temperature for another 1 h. Dimethyl malonate (86 µL, 0.75 mmol) and N,O-bis(trimethylsilyl)acetamide (186 µL, 0.75 mmol) were added subsequently. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under vacuum and the residue was passed through a short silica gel column (EtOAc/hexanes = 1:9) to give an oily product. The enantiomeric excess of the product was determined by HPLC (Chiralcel AD-H column, *i*-PrOH/hexane 10/90, 1.0 mL min^{-1}, 254 nm: $t_{(R)}$ = 11.8 min, $t_{(S)}$ = 16.8 min). The products of the allylic alkylations using ligands **6** and **7** were shown to have $[\alpha]^{26}_D$ = –16.2 (*c* 0.48, $CHCl_3$) and $[\alpha]^{26}_D$ = –17.1 (*c* 0.50, $CHCl_3$) respectively.

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