The asymmetric transfer hydrogenation of benzoylpyridine: preparation and crystal structure of chiral heterocyclic Schiff base ligands

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Two optically active heterocyclic imine ligands **3** (**3a** and **3b**) have been synthesised for the iridium catalysed asymmetric transfer hydrogenation of 4-benzoylpyridine. **3b** was characterised by single crystal X-ray diffraction analysis. The two ligands (**3a** and **3b**) were applied to Ir-catalysed asymmetric transfer hydrogenation of 4-benzoylpyridine using 2-propanol as a source of hydrogen. The results showed that the corresponding chiral alcohol could be obtained with moderate yield and enantioselectivity at an optimum temperature.

Keywords: asymmetric transfer hydrogenation, Schiff base, synthesis, chiral

Chiral heterocyclic Schiff bases are potential synthons and biologically active compounds as well as an important catalysts.[1–5] In our previous work,[6] we synthesised a series of novel ferrocenylimines containing Schiff base ligands and applied them to the asymmetric transfer hydrogenation of ketones which resulted in moderate yields and enantioselectivity.

We have now synthesised two chiral heterocyclic Schiff base ligands and applied them to the asymmetric transfer hydrogenation of 4-benzoylpyridine. The results show that Ir(I)-catalysed asymmetric transfer hydrogenation of 4-benzoylpyridine proceeded in moderate yield and with moderate enantioselectivity (65–72% yield after 4h, and 38–46% e.e.).

Results and discussion

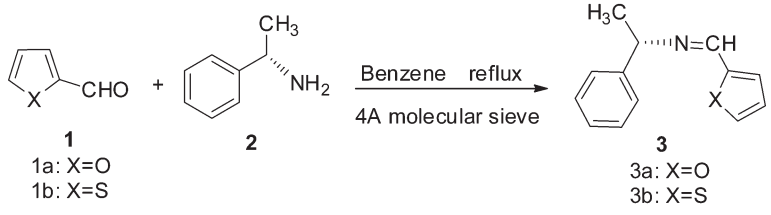
We studied the reaction of 2-furaldehyde, 2-thiophenecarbaldehyde (**la**, **1b**) with (S)-1- phenylethylamine. The reactions were carried out under the conditions used in our previous work[7], which are optimal of such condensations. In order to remove the water from the reaction we added 4Å molecular sieve to a water separator. The reaction was monitored by TLC until the almost complete conversion of the starting substrates into the desired products (Scheme 1).

The products were characterised by IR, ^{1}H NMR and MS. The spectroscopic data of the complexes were found to correspond with the expected structures. The imine function of the compounds was by strong absorption at about 1620 cm^{-1} in the IR-spectra, as well as by signals at about 8.10 and 8.35ppm in the ^{1}H NMR. Signals at 7.0–7.50 ppm belonged to the phenyl protons. The two ligands **3**(**3a–b**) were applied to Ir-catalysed asymmetric transfer hydrogenation of 4-benzoylpyridine using 2-propanol as a source of hydrogen. The results show that Ir(I)-catalysed asymmetric transfer hydrogenation of 4-benzoylpyridine resulted in moderate yield and moderate enantioselectivity(65–72% yield after 4h, and 38–46% e.e.). We speculated that the good catalytic activity of complex is due to the coordination of heterocyclic atoms of the heterocyclic imine ligands. The results obtained clearly demonstrate that chiral imine with heterocyclic ring is capable of activating Ir(I) towards catalytic transfer hydrogenation.

Single crystal X-ray diffraction analysis reveals that the molecular structure of compound **3b** is essentially as expected and confirms the formulation of the compound (Fig. 1). This compound is enantiomerically pure and crystallizes in the noncentrosymmetric P2(1) space group.

Table 1 Crystallographic data and structure refinement summary

CCDC deposit no.	741092
Empirical formula	$C_{13}H_{13}NS$,
Formula weight	215.30
Temoerature(K)	113(2)
Wavelength (Mo Ka) (A °)	0.71073
Crystal system	Monoclinic
Space group	*P2(1)*
Unit cell dimensions	
a (Å)	5.5337(11)
b (Å)	7.5238(15)
c (Å)	13.907(3)
Volume(Å ^{3})	577.2(2)
Z	2
Crystal size(mm)	0.20 x 0.18 x 0.16
Calculated density Mg m--	1.239
Absorption coefficient, mm-	0.246
F(000)	228
Reflections collected/unique	3861/1879 [R(int) = 0.0390]
Completeness to theta = 24.98	99.5 %
Data/restraints/parameters	1879/1/137
Limiting indices	–6<=*h*<=6, –8<=*k*<=8, –16<=*l*<=14
Goodness of fit on F2	0.990
Final R indices [I>2sigma(I)]	R^1 = 0.0326, wR^2 = 0.0739
R indices (all data)	R^1 = 0.0382, wR^2 = 0.0770
Absolute structure parameter	–0.05(8)
Largest diff. peak and hole/ e.A^{-3}	0.164 and –0.244



1
1a: X=O
1b: X=S

2

3
3a: X=O
3b: X=S

Scheme 1 Preparation of the chiral heterocyclic imine ligands **3**.

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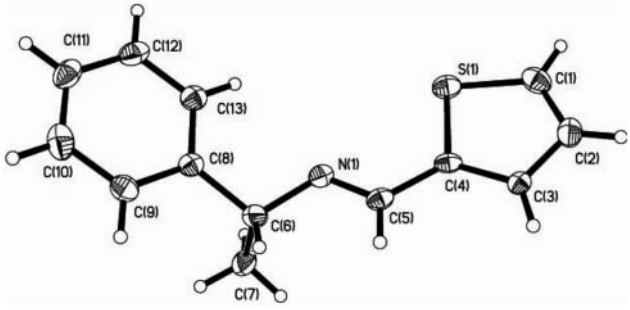


Fig. 1 The ORTEP structure of the title compound with atom labelling.

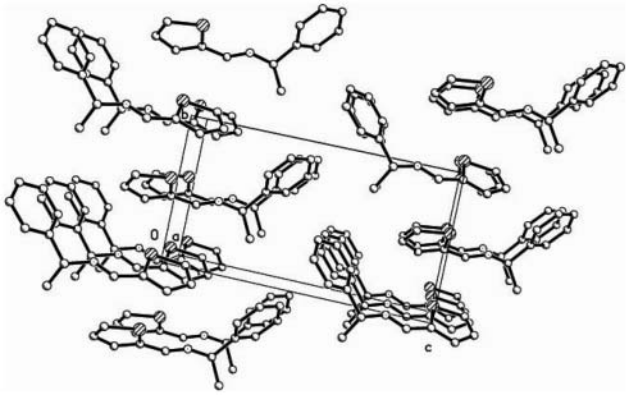


Fig. 2 Three-dimensional molecular-packing diagram of the title compound.

Table 2 Selected bond lengths (Å) and angles (deg) for **4**

Bond	Distance	Bond angle	deg
S(1)–C(1)	1.712(2)	C(2)–C(3)–C(4)–C(5)	–179.1(2)
S(1)–C(4)	1.726(2)	C(1)–S(1)–C(4)–C(5)	179.20(18)
N(1)–C(5)	1.266(3)	C(6)–N(1)–C(5)–C(4)	179.58(18)
N(1)–C(6)	1.463(3)	C(3)–C(4)–C(5)–N(1)	–177.8(2)
C(4)–C(5)	1.455(3)	S(1)–C(4)–C(5)–N(1)	3.6(3)
C(6)–C(8)	1.517(3)	C(5)–N(1)–C(6)–C(8)	142.2(2)
C(6)–C(7)	1.530(3)	N(1)–C(6)–C(8)–C(9)	–158.7(2)
C(1)–C(2)	1.344(3)	N(1)–C(6)–C(8)–C(13)	25.3(3)
C(3)–C(4)	1.385(3)	C(4)–S(1)–C(1)–C(2)	–0.2(2)

View of compound **3b** parallel to the thiophene and phenyl plane demonstrates the "Y" shape of the molecule (Fig. 2.), with the substituents adopting stable E-configuration. As shown by the crystal data, the C=N unit are conjugation with the thiophene ring (Table 2).

Experimental

All reactions were carried out under argon and monitored by TLC. Diethyl ether was dried using Na under reflux. Melting point (uncorrected) was measured with a XT4 melting point apparatus. ^{1}H NMR spectra were recorded on a Varian Mercury plus 300 MHz spectrometer, using $CDCl_3$ as solvent and TMS as the internal standard. Optical rotations were measured on a WZZ-3 polarimeter. The aldehydes were purified by vacuum distillation prior to use.

Synthesis of **3***; general procedure*

The aldehyde and amine were added followed by freshly dried molecular sieves. The mixture was maintained at reflux, periodically taking samples and analysing them by TLC. After some time depending on the substrate, the starting reagents were almost completely converted to the corresponding products. At the end of the reaction, the sieves were filtered off and washed with benzene. The filtrate was evaporated under reduced pressure. The product is purified by vacuum distillation or by recrystallisation from hexane.

N-phenylethyl-2-furfuraldehyde-imine **(3a):** Yellow oil (yield 61%), ($[\alpha]_D^{20}$+71.6 (c 1.5, CH_2Cl_2). (lit.[8] $[\alpha]_D^{20}$+76.4 (c 1.1, $CHCl_3$). The IR spectrum indicated the presence of the 1621 cm^{-1}(N=CH); ^{1}H NMR spectrum ($CDCl_3$) δ_H: (ppm) 1.55 (3H, d, J = 7 Hz, CH_3); 4.44 (IH, q, J = 5 Hz, CHN); 6.42 (1H, m, FurH-4); 6.69 (IH, d, J = 5 Hz, FurH-3); 7.1–7.4 (5H, m, Ph); 7.47 (IH, d, J = 2 Hz, FurH-5); 8.10 (1H, s, CH=N). MS (EI): 199.

N-phenylethyl-2-thiopheneformaldehyde-imine **(3b):** White crystal (yield 56%). M.p. 52–53 °C, ($[\alpha]_D^{20}$ +159.6 (c 3.6, CH_2Cl_2). (lit.[9] $[\alpha]_D^{20}$+183.4 (c 9.7, acetone). The IR spectrum indicated the presence of the 1621 cm^{-1} (N=CH); ^{1}H NMR spectrum ($CDCl_3$) δ_H: (ppm) 1.53 (3H, d, J = 7 Hz, CH0; 4.47 (1H, q, J = 7 Hz, CHN); 7.00 (IH, dd, J = 5 and 4 Hz, ThH-4); 7.0–7.5 (7H, m, Ph, ThH-3,5); 8.38 (IH, s, CH=N). MS (EI): 215.

X-ray crystal-structure analysis of **3b**

Crystals suitable for X-ray structure determination were obtained from the filtration by slow evaporation of the solvent. The determination of unit cell parameters and data collections was performed with MoKα radiation (λ = 0.71073 Å) and unit cell dimensions were obtained with least-squares refinements. The structure was solved by direct methods with SHELXL-97 program[10] and all data were corrected by using semi-empirical absorption corrections (SADABS) method. All the other non-hydrogen atoms were located by successive difference Fourier syntheses. The final refinement was carried out by full matrix least-squares methods with anisotropic thermal parameters for non-hydrogen atoms on F^2. The hydrogen atoms were added theoretically, and riding on the concerned atoms and refined with fixed thermal factors. Further details of the structure analyses are given in Table 1.

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publications (no. CCDC-741092). Copies of available materials can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retreiving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK, fax: +44-1223-336033; or deposit@ccdc.cam.ac.

Application of these new chiral ligands in Ir-catalysed asymmetric transfer hydrogenation

The catalyst was generated *in situ* by refluxing ligand **3a–b** (1.0 mmol%) with $[Ir(COD)Cl]_2$ (1.0 mmol%) in 2-propanol at 50°C under argon for 4h. After being cooled down to room temperature, 4-benzoylpyridine (2.0 mmol) was added, followed by KOH (1.5 mg, 0.03 mmol) under argon. The transfer hydrogenation was conducted at desired temperature under argon for a given time. The resulting solution was purified by flash chromatography on a silica gel column eluted by petroleum ether/ethyl acetate (4/1) and the product was analysed by HPLC. The product of the reduction 4-pyridinebenzyl

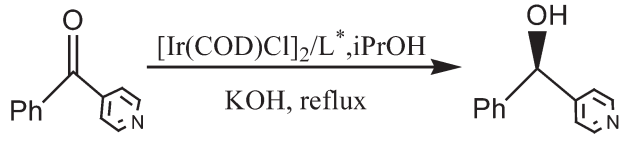
Table 3 Asymmetric transfer hydrogenation of benzoylpyridine in *i*-propanol catalysed by chiral Ir(I) complexes

Entry[a]	Ligand	Time/h	Temp/°C	Yield[b]/%	e.e./%[c]
1	**3a**	4	50	65	38
2	**3b**	4	50	72	46

[a] L:M:KOH:=1:1:2 (L= Ligand, M= Metal) $[Ir(COD)Cl_2]$

[b] Yield was calculated as alcohol after chromatography.

[c] e.e. values were determined by HPLC analysis of the isolated alcohol with Chiralcel OD columns. The HPLC conditions were: room temperature, mobile phase: *n*-hexane/isopropanol (80/20).



Scheme 2 Asymmetric transfer hydrogenation.

alcohol is white solid. ^{1}H NMR spectrum ($CDCl_3$) δ_H: (ppm) 5.76 (1H, s, CHOH); 6.51 (IH, s,OH); 7.30–7.41 (5H, m, Ph); 7.12 (2H, d, pyridine); 8.32 (2H, d, pyridine).

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