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LETTER

Synthesis of optically active Schiff base ligands from chiral 6-alkoxy-2-pyridinecarboxaldehydes and their application in rhodium catalyzed hydrosilations

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The area of catalytic asymmetric hydrosilation of ketones was developed within a short time period utilizing chiral phosphorus ligands [1], but current research centers on the use of nitrogen-based ligands [2]. Optically active pyridine and pyrrole imines [3] and oxazolines [4] have been used successfully in the asymmetric hydrosilation of prochiral ketones.

While a C_2 axis of symmetry has in general been demonstrated to increase the enantioselectivity of asymmetric hydrogenation catalysts, it is not necessary to obtain high *ee* values in hydrosilation reactions [4, 5]. Ligands without C_2 symmetry that are of particular interest to us are the pyridyl imine ligands prepared by Brunner and Riepl [6] where the chiral center of the ligand only influences one side of the metals coordination sphere. We were interested in determining if a chiral alkoxy group in the 6-position of the pyridine ring would enhance the asymmetric induction for the catalyst. With the recent synthesis of a new series of optically active 6-alkoxy-2-pyridinecarboxaldehydes (**2**) [7] we had in hand the necessary materials to prepare the six-substituted Schiff base ligands. Herein we report the synthesis of the new Schiff base ligands **3** and **4** and explore their utility in the asymmetric rhodium(I) catalyzed hydrosilation of acetophenone.

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Experimental

General

All manipulations of compounds and solvents were carried out using standard Schlenk techniques. Solvents were degassed and purified by distillation under nitrogen from standard drying agents [8]. Spectroscopic measurements utilized the following instrumentation: ^{1}H NMR, Varian XL 300; ^{13}C NMR, Varian XL 300 (at 75.4 MHz). NMR chemical shifts are reported in δ versus Me_4Si in ^{1}H NMR and assigning the $CDCl_3$ resonance at 77.00 ppm in ^{13}C spectra. Optical rotations were measured at ambient temperature (20 ± 1 °C) on a Perkin-Elmer 241 polarimeter using the sodium D-line. The instrument was calibrated using optically pure 1-phenylethanol (Aldrich) at concentrations ranging from 0.05 to 1.0 g/ml in dichloromethane. The (*R*)- and (*S*)-α-methylbenzylamines, n-BuLi (2.5 M in hexanes) and all optically active alcohols were purchased from Aldrich Chemical Company and used as received. The 2,6-dibromopyridine was purchased from Lancaster Synthesis and used as received. The nickel(II) bromide was purchased from Alfa. $(MeCN)_2NiBr_2$ [9], $[(COD)RhCl]_2$ [10], **1** [7] and **2** [7] were prepared by literature methods. The acetophenone was distilled from barium oxide and the diphenylsilane was distilled from CaH_2 prior to use and stored under nitrogen. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Preparation of optically-active imines (3 and 4)

(*R*)- or (*S*)-α-Methylbenzylamine (5 mmol, 0.61 g) and the appropriate 6-alkoxy-2-pyridinecarboxaldehyde (5 mmol) were added to a benzene solution containing 10-camphorsulfonic acid (approximately 10 mg). The mixture was heated at reflux for 2 h and then allowed to cool. The mixture was dried over K_2CO_3, filtered, and the solvent removed under reduced pressure to afford crude **3a–e** and **4a–e** (97–100%). A $CHCl_3$ (20 ml) solution of **3b–d**, **4a**, **4c** or **4d** was treated with $(CH_3CN)_2NiBr_2$ (1.5 g, 5.0 mmol) and stirred at ambient temperature for 1 h. The solution was filtered through a Celite to remove the excess $(CH_3CN)_2NiBr_2$ and the complexes precipitated by adding ether (150 ml) and pet ether (15 ml). The complexes were collected on a glass frit and washed with ether (2 × 50 ml). The precipitate was redissolved in $CHCl_3$ and extracted with 10% NaCN (30 ml). The $CHCl_3$ layer was quickly drained into a flask containing K_2CO_3. The mixture was filtered, the solvent removed, and the oil redissolved in ether (5 ml). The ether solution was passed through a pasteur-pipet filled with Florisil and then the solvent removed under reduced pressure to afford pure **3b–d**,

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4a, **4c** and **4d** in 56–75% yield. In the cases of **3a**, **3e**, **4b** and **4e**, the crude imines were recrystallized from pentane at −25 °C (60–78%).

6-[(1R,2S,5R)-Mentoxyl]-N-[(1S)-1-(1-phenyl)ethyl]-2-picolinimine (3a)

^{1}H NMR ($CDCl_3$) δ 8.34 (s, 1 H), 7.68–7.21 (m, 7 H), 6.68 (dd, J = 8.1, 1.0 Hz, 1 H), 5.05 (dt, J = 10.8, 4.4 Hz, 1 H), 4.60 (q, J = 6.6 Hz, 1 H), 2.20 (m, 1 H), 2.03 (m, 1 H), 1.71 (m, 2 H), 1.60 (d, J = 6.6 Hz, 3 H), 1.58–1.45 (m, 2 H), 1.25–0.96 (m, 3 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.89 (d, J = 7.1 Hz, 3 H), 0.74 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.5, 161.0, 152.4, 145.0, 138.8, 128.4 (2 C), 126.9, 126.6 (2 C), 113.4, 112.3, 74.5, 69.6, 47.8, 40.9, 34.5, 31.4, 26.2, 24.8, 23.7, 22.2, 20.8, 16.6. *Anal.* Calc. for $C_{24}H_{32}N_2O$: C, 79.08; H, 8.85. Found: C, 79.16; H, 8.91%.

6-[(1R,2S,5R)-Menthoxy]-N-[(1R)-1-(1-phenyl)ethyl]-2-picolinimine (4a)

^{1}H NMR ($CDCl_3$) δ 8.34 (s, 1 H), 7.68–7.21 (m, 7 H), 6.69 (dd, J = 8.1, 0.9 Hz, 1 H), 5.05 (dt, J = 10.6, 4.3 Hz, 1 H), 4.60 (q, J = 6.6 Hz, 1 H), 2.21–2.00 (m, 2H), 1.76–1.68 (m, 2 H), 1.60 (d, J = 6.6 Hz, 3 H), 1.56–1.46 (m, 2 H), 1.26–0.94 (m, 3 H), 0.91 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 7.0 Hz, 3 H), 0.77 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.5, 161.0, 152.4, 145.0, 138.8, 128.4 (2 C), 126.9, 126.6 (2 C), 113.4, 112.3, 74.5, 69.6, 47.8, 40.8, 34.6, 31.4, 26.3, 24.8, 23.7, 22.2, 20.8, 16.6. *Anal.* Calc. for $C_{24}H_{32}N_2O$: C, 79.08; H, 8.85. Found: C, 79.03; H, 8.85%.

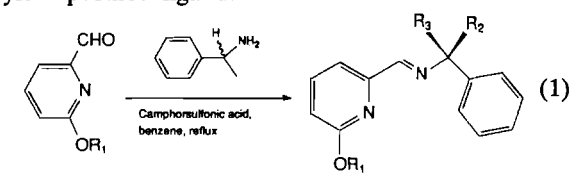
Hydrosilation of acetophenone

A Schlenk tube was charged with acetophenone (0.6 g, 5 mmol), $[(COD)RhCl]_2$ (12.3 mg, for 100/1, substrate/Rh, mol/mol), the appropriate imine ligand and dichloromethane (3 ml). The mixture was degassed by three consecutive freeze–pump–thaw cycles. A separate Schlenk tube was charged with diphenylsilane (1.3 ml, 7 mmol) and dichloromethane (1 ml) and degassed as above. The latter solution was cannulated into the acetophenone mixture and allowed to react at 0 °C until the carbonyl band in the infrared (1685 cm^{-1}) disappeared (~18 h). The mixture was then diluted with acetone (5 ml) and 10% hydrochloric acid (10 ml) and then stirred vigorously for 2 h. The mixture was extracted with ether and the organic layer dried over K_2CO_3. The ether was removed and the crude product purified by bulb–bulb distillation (fraction from 60–80 °C, 0.7 torr, was collected).

Results and discussion

Ligand synthesis and characterization

Various chiral 6-alkoxy-2-pyridinecarboxaldehydes were condensed with (*R*)-α-methylbenzylamine in the presence of a catalytic amount of 10-camphorsulfonic acid in benzene to yield the appropriate 6-[alkoxy]-*N*-[(*1R*)-1-(1-phenyl)ethyl]-2-picolinimine ligands (**3**) or (*S*)-α-methylbenzylamine to yield 6-[alkoxy]-*N*-[(*1S*)-1-(1-phenyl)ethyl]-2-picolinimines (**4**). A small amount of unreacted amine and/or aldehyde was present in the crude product, and was removed by recrystallization in the cases of **3a**, **3e**, **4b** and **4e**, which are solids. However, in the cases of the remaining ligands, which are highly viscous oils, purification was achieved by nickel(II) bromide complexation, followed by several washes of the precipitated complex with ether. The ligands were then released from the metal using 10% aqueous NaCN and subjected to filtration through Florisil to yield purified ligand.

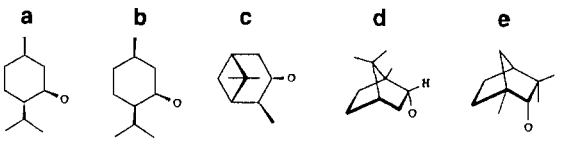


(1)

2

3; R_2 = H, R_3 = Me

4; R_2 = Me, R_3 = H



To structurally characterize the ligands a single-crystal X-ray study was carried out on compound **3e**. Crystals of **3e** suitable for X-ray analysis were obtained from a saturated pentane solution which was cooled to −25 °C and allowed to stand for several days. A plot of **3e** and the atomic labeling scheme are displayed in Fig. 1. From the structure it is apparent that the alkoxy group in the 6-position of the pyridine ring will have significant interaction with the metal upon complexation.

Hydrosilation of acetophenone

The effectiveness of these ligands in the rhodium-catalyzed asymmetric hydrosilation of acetophenone with diphenylsilane (eqn. (2)) was investigated using several substrate/rhodium and ligand/rhodium ratios (Table 1). The hydrosilation reactions proceeded smoothly at 0 °C (complete in less than 18 h), but low *ee* values were observed. A large excess of ligand appeared necessary to obtain even low asymmetric induction. This is in direct contrast to phosphorus-based ligands where a 1/1 ratio of ligand/metal is

TABLE 1. Results for the hydrosilation of acetophenone using ligands **3** and **4** with $[(COD)RhCl]_2$

Entry	Ligand	Substrate/Rh ratio	Ligand/Rh ratio	Optical yield (% *ee*)
1	**3a**	200/1	5/1	2.4 (*S*)
2	**3b**	200/1	5/1	0.4 (*S*)
3	**3c(i)**	200/1	5/1	6.1 (*S*)
4	**3d**	200/1	5/1	3.8 (*R*)
5	**3e**	200/1	5/1	5.4 (*S*)
6	**3e**	100/1	10/1	2.5 (*R*)
7	**4a**	200/1	5/1	2.7 (*S*)
8	**4b**	200/1	5/1	0.5 (*S*)
9	**4c(i)**	200/1	5/1	0.8 (*S*)
10	**4d**	200/1	5/1	1.1 (*R*)
11	**4e**	200/1	5/1	0.9 (*S*)

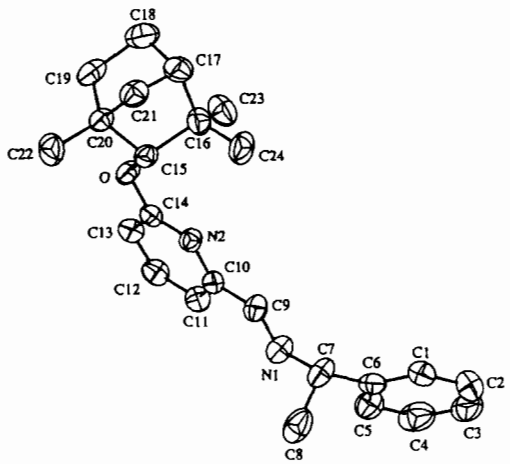
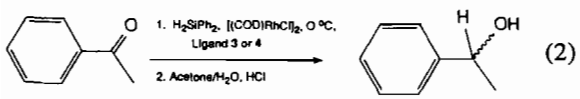


Fig. 1. Molecular structure of crystalline **3e** showing atomic labeling scheme.

most effective but is a consistent need for all chiral nitrogen based ligands. A noteworthy point in the data is the configurational change in the product as a function of the ligand/rhodium and substrate/rhodium ratios (Table 1, entries 5 and 6). This characteristic is not uncommon for nitrogen based ligands in the rhodium catalyzed hydrosilation reaction.



(2)

80-84% Chemical Yield

Supplementary material

Full spectroscopic and analytical data for compounds **1a**, **2a**, **3b–e**, **4b–e**, and a crystallographic report (tabular form) containing bond lengths, bond angles, positional parameters for non-hydrogen and hydrogen atoms, anisotropic thermal parameters, and a listing of structural factors for the single-crystal X-ray diffraction study of **3e** (23 pages) are available from the authors on request.

Acknowledgements

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