Kinetic Resolution of Pyridyl Alcohols by Cu(II)(Borabox)-Catalyzed Acylation

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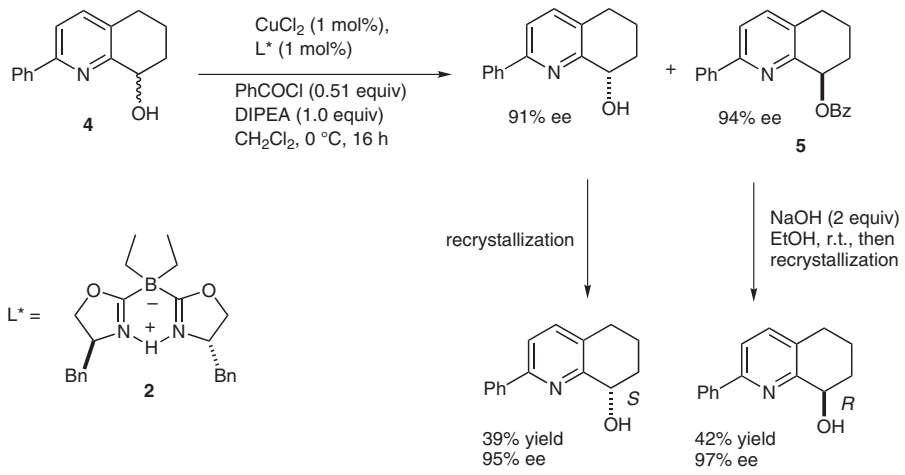
Abstract: Kinetic resolution of pyridyl alcohols has been achieved using copper(II)(borabox)-catalyzed benzoylation. Selectivity factors (k_{rel}) of up to 125 have been observed and application to the synthesis of chiral pyridyl phosphine ligands is described.

Key words: kinetic resolution, asymmetric catalysis, copper, bisoxazoline ligands, pyridines



Scheme 1 Preparative scale pyridyl alcohol resolution

Chiral pyridyl alcohols are valuable intermediates in the synthesis of ligands for asymmetric catalysis,[1] chiral nucleophilic catalysts,[2] and biologically active compounds.[3] Our interest in the asymmetric synthesis of pyridyl alcohols arose because cationic iridium complexes **1** containing chiral P,N-ligands which are derived from pyridyl alcohols are highly selective catalysts for asymmetric hydrogenation of unfunctionalized olefins (Figure 1).[1] Literature approaches to their asymmetric synthesis have focused on enantioselective reduction of the corresponding ketones,[4] although enzymatic resolution has also been reported.[5] We have recently found that chiral boron-bridged bisoxazolines (borabox) are efficient ligands for the kinetic resolution of 1,2-diols and pyridyl alcohols through Cu-catalyzed acylation.[6] Herein, we describe the use of this method for the synthesis of enantiomerically enriched pyridyl alcohols, with very high selectivities being achieved in some cases.

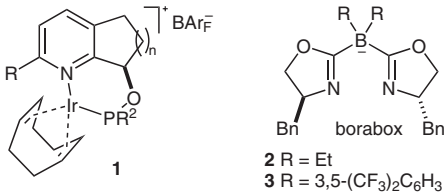


Figure 1 Pyridyl alcohol derived iridium complexes for catalytic asymmetric hydrogenation and borabox ligands for alcohol resolution (BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate)

For example, kinetic resolution of pyridyl alcohol **4** was carried out efficiently using the readily available borabox ligand **2** (Scheme 1).[7] Benzoylation under optimized conditions (1 M, CH_2Cl_2, 1 mol%, 0 °C, 16 h) was followed by column chromatography on silica gel to separate the alcohol and benzoate. The alcohol was recovered with an ee of 91% *S* and subsequent recrystallization from hexane–EtOAc provided *S*-alcohol in 39% yield and 95% ee. The benzoate **5** was isolated with 94% ee *R*. This corresponds to an *S* value of 100.[8] Reducing the amount of $CuCl_2$ and ligand **2** to 0.5 mol% resulted in a decrease in selectivity (*S* = 25). Benzoylation of **4** using 1 mol% catalyst at

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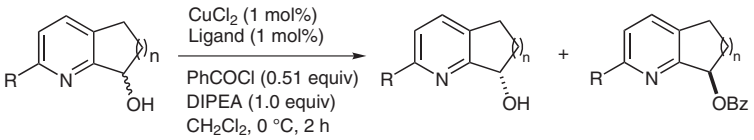
Table 1 Enantioselective Benzoylation of Various Pyridyl Alcohols



6 R = H n = 1
7 R = Ph n = 1
8 R = H n = 2
4 R = Ph n = 2
9 R = Cl n = 2

Substrate	Ligand	Alcohol ee (%)[a]	Benzoate ee (%)[a]	Conversion (%)[b]	S (k_{rel})[b]
6	**2**	16	33	33	2
6	**3**	5	5	46	1
7	**2**	50	84	36	18
7	**3**	76	91	45	51
8	**2**	99	60	62	9
8	**3**	83	76	52	19
4	**2**	61	96	39	92
4	**3**	70	97	42	125
9	**2**	62	80	44	17
9	**3**	58	65	47	8

[a] HPLC assay.
[b] Reference 8.

–24 °C and 22 °C also resulted in reduced selectivities (S = 18 and 46, respectively).

Hydrolysis of the benzoate **5** was accomplished without racemization (NaOH, EtOH, r.t.) to yield the *R*-alcohol in 42% yield and 97% ee after recrystallization from hexane–EtOAc. A straightforward synthesis of both enantiomers of the ligand precursor **4** has thus been accomplished, with the borabox ligand **2** inducing very high enantioselectivity.

The scope of this method was determined by benzoylation of various pyridyl alcohols (Table 1). The selectivities obtained were highly dependent on the structure of the substrate. A comparison of pyridyl alcohols **6** and **7** shows that substitution at the α-CH of the pyridine ring with a phenyl group greatly enhances the selectivity. During benzoylation of pyridyl alcohol **7** both borabox ligands tested impart levels of enantioselectivity, which are useful synthetically, with an S value of 51 for ligand **3**. Substrate **8** is benzoylated with an S value of 19 using ligand **3**, indicating that when a six-membered ring is fused to the pyridine ring the enantioselectivity can be higher than that of a five-membered ring analogue. As described above, benzoylation of substrate **4**, containing a phenyl group α to the pyridine N atom and a six-membered ring, was highly enantioselective with both borabox ligands, giving S values of around 100. Substrate **9**, containing an α-chloro substituent, exhibited similar selectivities to the unsubstituted analogue **8**. It is also of note that use of an analogous dimethylmethylene-bridged bisoxazoline (box) complex did not result in efficient resolution for any of the substrates.

In conclusion, we have developed an efficient and convenient method for the kinetic resolution of pyridyl alcohols using Cu(II)(borabox)-catalyzed benzoylation, which allows straightforward access to pyridyl alcohols in high enantiomeric excess.

NMR spectra were recorded on 400 MHz and 500 MHz Bruker Avance spectrometers. Mass spectra were recorded using Finnigan MAT spectrometers. Elemental analyses were obtained from the Micro-Analytical Laboratory of the Department of Chemistry at the University of Basel. Optical rotations were measured on a Perkin-Elmer polarimeter 341 equipped with a Na-lamp. Melting points were recorded on a Büchi 535 apparatus and are uncorrected. Anhyd CH_2Cl_2 was obtained by distillation from CaH_2 under N_2 or directly from Fluka. All other reagents were purchased from Fluka and used as received. Chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). TLC was carried out using Macherey-Nagel silica gel plates. Pyridyl alcohols **4**,[9] **6**,[10] **7**,[11] **8**,[5c] **9**,[12] and borabox ligands[6a] were prepared according to literature procedures.

Gram-Scale Synthesis of Both Enantiomers of 8-Hydroxy-2-phenyl-5,6,7,8-tetrahydroquinoline

Anhyd $CuCl_2$ (6.0 mg, 1 mol%) and ligand **2** (17.3, mg, 1 mol%) were dissolved in anhyd CH_2Cl_2 (5 mL) and stirred for 90 min at r.t. under argon. The resulting dark yellow solution was filtered through a syringe filter (CHROMAFIL O-20/15 MS 0.2 μM, Macherey-Nagel) into a dry Schlenk tube containing racemic 8-hydroxy-

2-phenyl-5,6,7,8-tetrahydroquinoline (**4**; 1.0 g, 4.44 mmol) under argon. The resulting green solution was cooled to 0 °C in an ice bath. DIPEA (773 μL, 1.0 equiv) was added dropwise, to give a blue/green solution, followed by benzoyl chloride (284 μL, 0.55 equiv). The mixture was stirred overnight, during which time it was allowed to warm slowly to r.t. H_2O (5 mL) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The benzoate and alcohol were separated by column chromatography (15 cm × 2.5 cm, 10:1 pentane–EtOAc) to give the *R*-benzoate (694 mg, 47%, 94% ee) as a pale green oil and the *S*-alcohol (426 mg, 43%, 91% ee) as a pale green crystalline solid. The alcohol was purified further by recrystallization from hot 1:1 hexane–EtOAc to give 387 mg (39%) of *S*-alcohol in 95% ee as colorless prisms; mp 88–90 °C.

_S_-Alcohol 4

R_f = 0.13 (9:1 pentane–EtOAc); $[\alpha]_D^{20}$ +143.0 (*c* = 1.0 in CH_2Cl_2). HPLC (Chiralcel OD-H, 0.46 cm × 25 cm): Heptane–*i*-PrOH (96:4), 0.5 mL/min, 20 °C); t_R (min) = 23.5 (*R*), 21.0 (*S*).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (2 H, m), 7.58 (1 H, d, *J* = 8.0 Hz), 7.35–7.50 (4 H, m), 4.75 (1 H, dd, *J* = 9.1, 5.8 Hz, CHO), 4.38 (1 H, br s, OH), 2.80–2.93 (2 H, m), 2.33–2.43 (1 H, m), 1.96–2.10 (1 H, m), 1.75–1.92 (2 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 154.6, 139.1, 138.3, 130.4, 129.3, 129.1, 127.1, 119.7, 69.5, 31.0, 28.4, 20.1.

MS (EI): *m*/*z* (%) = 225 (M^+, 15), 196 (30), 169 (100).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.57; H, 6.76; N, 6.08.

_R_-Benzoate 5

R_f = 0.26 (9:1 pentane–EtOAc); $[\alpha]_D^{20}$ –147.8 (*c* = 1.0 in CH_2Cl_2). HPLC (Chiralcel OD-H, 0.46 cm × 25 cm): Heptane–*i*-PrOH (96:4), 0.5 mL/min, 20 °C); t_R (min) = 17.0 (*R*), 33.8 (*S*).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (2 H, m), 7.94–7.97 (2 H, m), 7.63 (1 H, d, *J* = 8.1 Hz), 7.52–7.56 (2 H, m), 7.31–7.44 (5 H, m), 6.33 (1 H, t, *J* = 5.1 Hz, CHO), 2.95 (1 H, dt, *J* = 16.9, 5.6 Hz, Ar-CH_aH$_b$), 2.84 (1 H, dd, *J* = 16.9, 8.8, 5.8 Hz, ArCH$_a$$H_b$), 2.29–2.34 (1 H, m), 2.17–2.25 (1 H, m), 2.05–2.11 (1 H, m), 1.89–1.97 (1 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6 (C=O), 155.4, 153.6, 139.4, 138.2, 133.1, 132.2, 131.4, 130.2, 129.1, 129.0, 128.7, 127.1, 120.0, 72.2 (CHO), 29.6, 28.6, 19.2.

MS (FAB): *m*/*z* (%) = 330 (M + H^+, 85).

Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.32; H, 5.63; N, 4.27.

Hydrolysis of _R_-Benzoate 5

R-Benzoate **5** (330 mg, 1 mmol, 94% ee) was dissolved in EtOH (20 mL) and 2 N aq NaOH (1 mL, 2 mmol, 2 equiv) was added at r.t. After stirring for 3 h, the mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give the crude *R*-alcohol **4** as a crystalline solid (93% ee). Recrystallization from hot 1:1 hexane–EtOAc gave 200 mg (89%) of the *R*-alcohol **4** with 97% ee; mp 85–94 °C.

The absolute configuration of pyridyl alcohols **7** and **8** was assigned by comparison of the $[\alpha]_D$ values with those previously reported in the literature.[1e,5c] The absolute configurations of the pyridyl alcohols **4** and **6** were determined by conversion to the corresponding [iridium (COD)]BAr_F complexes **1** which were analyzed by X-ray diffraction.[13]

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