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# Efficient Chemoenzymatic Synthesis of Chiral Pincer Ligands

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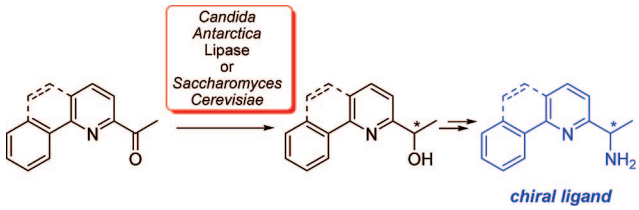


Chiral, nonracemic pincer ligands based on the 6-phenyl-2-aminomethylpyridine and 2-aminomethylbenzo[*h*]quinoline scaffolds were obtained by a chemoenzymatic approach starting from 2-pyridyl and 2-benzoquinolyl ethanone. In the enantiodifferentiating step, secondary alcohols of opposite absolute configuration were obtained by a baker's yeast reduction of the ketones and by lipase-mediated dynamic kinetic resolution of the racemic alcohols. Their transformation into homochiral 1-methyl-1-heteroarylethanamines occurred without loss of optical purity, giving access to pincer ligands used in enantioselective catalysis.

Metal complexes of general structure **1,** in which ruthenium(II) and osmium(II) are bound to a diphosphine and a bi- or tricyclic, aminomethylpyridine-based, *C,N,N*-terdentate ligand (CNN pincer), have recently been shown to be extremely efficient catalysts for the catalytic reduction of aromatic ketones.[1] Ruthenium(II) complexes, in which the CNN pincer ligand **2** (R = Me) is present in combination with different diphosphines, are the most active catalysts in the transfer hydrogenation of alkyl aryl ketones in 2-propanol, displaying turnover frequencies of up to $10^6$ $h^{-1}$ at remarkably low catalyst loadings (0.005−0.001 mol %).[1a] Moreover, Ru(II)[1b] and Os(II)[1c] complexes containing the chiral CNN ligands (*R*)-**3** and

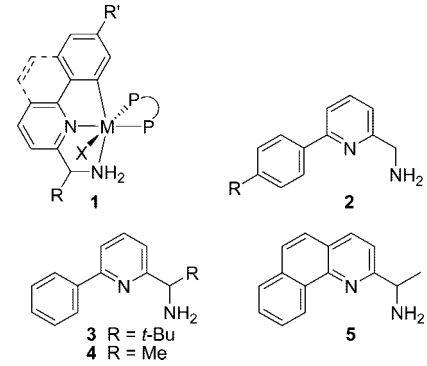


**FIGURE 1.** CNN pincer ligands and metal complexes.

(*R*)-**4** gave high enantioselectivities (up to 98% ee of the alcohol products) in the transfer hydrogenation of prochiral ketones. The Os(II) derivatives are also excellent catalysts for the asymmetric hydrogenation of ketones.[1c] More recently,[1d] comparably high enantioselectivities and productivities have been obtained with Ru and Os complexes prepared from the racemic tricyclic benzo[*h*]quinoline ligand **5** and chiral diphosphanes.

On account of their importance as scaffolds for chiral ligands and as bioactive compounds,[2] the synthesis of chiral aminoalkylpyridines is of special interest. Common approaches based on asymmetric synthesis include the addition of organometallics to chiral imines,[3] the enantioselective catalytic reduction of imines[4] and hydrazones,[5] and the catalytic hydroamination of alkenes.[6]

The synthesis of chiral ligands (*R*)-**3** and (*R*)-**4** via the diastereoselective reduction of chiral *N*-*p*-toluenesulfinyl ketimines was reported by Chelucci et al.[7] However, replacement of the bulky *t*-butyl group of (*R*)-**3** with the methyl of (*R*)-**4** dramatically decreased the stereoselectivity. An alternative approach to (*R*)-**4** was also described,[7c] via mesylation of the corresponding (*S*)-alcohol **8**, obtained from a chiral precursor, and displacement with azide; this method, however, suffered from a significant loss of enantiopurity in the substitution step.

Biocatalysis with whole cell systems and isolated enzymes provides a clean and ecological alternative for the synthesis of a variety of chiral building blocks with high degree of selectivity under mild reaction conditions.[8]

Enantiomerically pure secondary alcohols, in particular, can be efficiently obtained by lipase-catalyzed resolution of the

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(1) (a) Baratta, W.; Chelucci, G.; Gladiali, S.; Siega, K.; Toniutti, M.; Zanette, M.; Zangrando, E.; Rigo, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 6214–6219. (b) Baratta, W.; Bosco, M.; Chelucci, G.; Del Zotto, A.; Siega, K.; Toniutti, M.; Zangrando, E.; Rigo, P. *Organometallics* **2006**, *25*, 4611–4620. (c) Baratta, W.; Ballico, M.; Chelucci, G.; Siega, K.; Rigo, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4362–4365. (d) Baratta, W.; Ballico, M.; Baldino, S.; Chelucci, G.; Herdtweck, E.; Siega, K.; Magnolia, S.; Rigo, P. *Chem.—Eur. J.* **2008**, *14*, 9148–9160.

(2) See for example: (a) Lawson, E. C.; Hoekstra, W. J.; Addo, M. F.; Andrade-Gordon, P.; Damiano, B. P.; Kauffman, J. A.; Mitchell, J. A.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2619–2622. (b) Lloyd, G. K.; Williams, M. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 461–467. (c) Wu, J. H.; Zamir, L. O. *Anti-Cancer Drug Des.* **2000**, *15*, 73–78.

(3) Alvaro, G.; Pacioni, P.; Savoia, D. *Chem.—Eur. J.* **1997**, *3*, 726–731.

(4) (a) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226–236. (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069. (c) Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713–715.

(5) Burk, M. J.; Martinez, J. P.; Feaster, J. E.; Cosford, N. *Tetrahedron* **1994**, *50*, 4399–4428.

(6) (a) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367–391. (b) Roesky, P. W.; Mueller, T. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2708–2710.

(7) (a) Chelucci, G.; Baldino, S.; Chessa, S. *Tetrahedron* **2006**, *62*, 619–636. (b) Chelucci, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2353–2383. (c) Chelucci, G.; Cabras, M. A.; Saba, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1973–1978.

(8) Faber, K. *Biotransformations in Organic Chemistry*, 5th ed.; Springer: Berlin, 2004.

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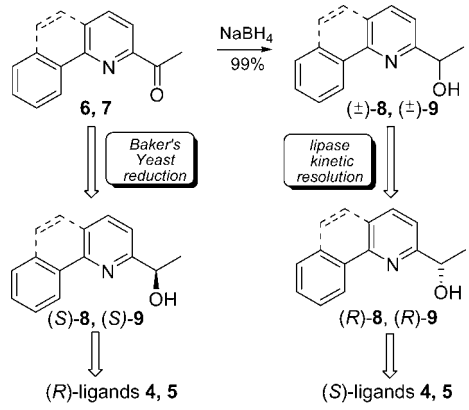
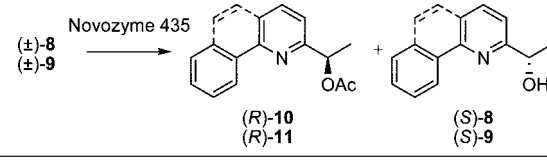
**SCHEME 1. General Strategy for the Synthesis of Chiral Nonracemic Pincer Ligands 4 and 5**




corresponding racemic mixtures[9] and by the asymmetric reduction of prochiral ketones with isolated dehydrogenases[10] or with baker's yeast (*Saccharomyces cerevisiae*).[11] Herein, we describe the application of these stereocomplementary biotransformations to the synthesis of both enantiomers of 1-(6-phenylpyridin-2-yl)ethanamine **4** (Scheme 1). (*S*)-**4** was obtained via the lipase-mediated kinetic resolution of the secondary alcohol (±)-**8,** while the baker's yeast (*Saccharomyces cerevisiae*) reduction of the ketone **6** gave access to the enantiomeric ligand (*R*)-**4**. This approach was then extended to the synthesis of the novel chiral 1-(benzo[*h*]quinolin-2-yl)ethanamine CNN pincer ligands (*R*)-**5** and (*S*)-**5**.

*Candida antarctica* lipase B (CAL-B) shows a very high and general specificity for the (*R*)-enantiomer in the acylation of chiral secondary alcohols[12] which has been fully explained at the molecular level.[13] The enantiospecific acylation of chiral amines by CAL-B has also been reported;[14] however, while the dynamic kinetic resolution (DKR)[15] of racemic *sec*-alcohols is well established, few protocols have been reported for the DKR of amines.[16] When we applied these conditions to the resolution of 6-substituted 2-(1-aminoethyl)pyridines, the resulting enantiospecificity was unsatisfactory, and harsh conditions were required for the recovery of amines from the resolved acetamides. Therefore, we decided to use CAL-B immobilized on polyacrylamide (Novozyme) for the kinetic resolution of the racemic alcohols **8** and **9** (Scheme 1).The alcohols were obtained by the $NaBH_4$ reduction of the corresponding ketones **6** and **7**. 2-Acetyl-6-phenylpyridine **6** was obtained by the Suzuki coupling of phenylboronic acid and 2-acetyl-6-bromopyridine,[17] while the 2-acetylbenzo[*h*]quinoline **7** was synthesized from 2-chlorobenzo[*h*]quinoline as reported.[1d]

**TABLE 1. Kinetic and DKR of Alcohols 8 and 9 with Novozyme 435**




| entry | substrate | *E* | conv. (%) | (*R*)-acetate ee % (yield %)[a] | | (*S*)-alcohol ee % (yield %)[a] | |
|---|---|---|---|---|---|---|---|
| 1 | (±)-**8**[b] | >500 | 46[c] | **10** | >99.9[d–f] (45) | **8** | 79[e] (50) |
| 2 | (±)-**9**[b] | >500 | 44[c] | **11** | >99[d,g] (40) | **9** | 86[g] (47) |
| 3 | (±)-**8**[h] | | 93[i] | **10** | >99.9 (70) | | |
| 4 | (±)-**9**[h] | | 92[i] | **11** | >99 (70) | | |

[a] Product isolated after chromatographic purification. [b] Kinetic resolution. Conditions: vinyl acetate, *t*-butyl methyl ether, rt. [c] Calculated conversion. [d] After hydrolysis. [e] By chiral high resolution gas chromatography (HRGC; β-cyclodextrine). [f] Lit.[18] 98%. [g] From the $^1$H NMR analysis of the corresponding Mosher's ester. [h] DKR. Conditions: *p*-chlorophenylacetate, toluene, 70 °C, 2% $Ru_2(CO)_4(\mu\text{-H})(C_4Ph_4\text{-}COHOCC_4Ph_4)$. [i] By HRGC.

The lipase-catalyzed asymmetric acetylation of **8**, with Novozyme and vinyl acetate in *t*-butylmethylether gave the corresponding (*R*)-acetate **10** with excellent enantioselectivity (enantiomeric ratio $E > 500$) and with recovery of the unreacted alcohol (*S*)-**8** (Table 1, entry 1), in agreement with literature data.[18] Similarly, the tricyclic alcohol **9** gave the corresponding (*R*)-acetate **11** in 40% yield (44% conversion) and ee > 99% ($E > 500$; Table 1, entry 2), while the recovered alcohol (*S*)-**9** had 86% ee.

Although the optical purity of the resolved acetates (*R*)-**10** and (*R*)-**11** was excellent (Table 1), their yield is intrinsically limited by the 50% maximum attainable in a kinetic resolution and by the need for a chromatographic separation of the enantioresolved alcohol and ester products. Both limitations were overcome by applying to the lipase-catalyzed transesterification of (±)-**8** and (±)-**9** the conditions developed by Bäckvall et al. for the dinamic kinetic resolution of *sec*-alcohols.[19] When the acetylation, with *p*-chlorophenylacetate as the acyl donor, was coupled to the in situ racemization of the slow reacting enantiomer with the Ru based redox catalyst $[Ru_2(CO)_4(\mu\text{-H})(C_4Ph_4\text{-}COHOCC_4Ph_4)]$ (Shvo's catalyst), the reaction reached complete conversion, enantioconverging to the (*R*)-acetates as unique products. These were isolated in 70% yield (not optimized) after column chromatography (Table 1, entries 3, 4).

(9) (a) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis: Regio-and Stereoselective Biotransformations*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2005. (b) Schmid, R. D.; Verger, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1608–1633.

(10) (a) Kroutil, W.; Mang, H.; Edegger, K.; Faber, K. *Curr. Opin. Chem. Biol.* **2004**, *8*, 120–126. (b) Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2659–2681. (c) Nakamura, K.; Matsuda, T. Reduction of Ketones. In *Enzyme Catalysis in Organic Synthesis*; Drauz, K., Waldmann, H., Eds.; Wiley-VCH: Weinheim, 2002; Vol. 3, pp 991−1047.

(11) (a) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071–1140. (b) Czuck, S.; Blanzer, B. I. *Chem. Rev.* **1991**, *91*, 49–97. (c) Servi, S. *Synthesis* **1990**, 1–25.

(12) Rotticci, D.; Hæffner, F.; Orrenius, C.; Norin, T.; Hult, K. *J. Mol. Catal. B: Enzym.* **1998**, *5*, 267–272. (b) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.

(13) (a) Mccabe, R. W.; Rodger, A.; Taylor, A. *Enzyme Microb. Technol.* **2005**, *36*, 70–74. (b) Uppenberg, J.; Ohrner, N.; Norin, M.; Hult, K.; Kleywegt, G. J.; Patkar, S.; Waagen, V.; Anthonsen, T.; Jones, T. A. *Biochemistry* **1995**, *34*, 16838–16851. (c) Uppenberg, J.; Hansen, M. T.; Patkar, S.; Jones, T. A. *Structure* **1994**, *2*, 293–308.

(14) (a) Ismail, H.; Madeira Lau, R.; van Rantwijk, F.; Sheldon, R. A. *Adv. Synth. Catal.* **2008**, *350*, 1511–1516. (b) van Rantwijk, F.; Sheldon, R. A. *Tetrahedron* **2004**, *60*, 501–519. (c) Skupinska, K. A.; McEachern, E. J.; Baird, I. R.; Skerlj, R. T.; Bridger, G. J. *J. Org. Chem.* **2003**, *68*, 3546–3551. (d) Torre, O.; Busto, E.; Gotor-Fernández, V.; Gotor, V. *Adv. Synth. Catal.* **2007**, *349*, 1481–1488. (e) Gotor-Fernández, V.; Busto, E.; Gotor, V. *Adv. Synth. Catal.* **2006**, *348*, 797–812. (f) Iglesias, L. E.; Sánchez, V. M.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1997**, *8*, 2675–2677.

(15) (a) Martín-Matute, B.; Bäckvall, J.-E. *Curr. Opin. Chem. Biol.* **2007**, *11*, 226–232. (b) Pamies, O.; Bäckvall, J.-E. *Trends Biotechnol.* **2004**, *22*, 130–135. (c) Pamies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247–3262. (d) Faber, K. *Chem.—Eur. J.* **2001**, *7*, 5005–5010.

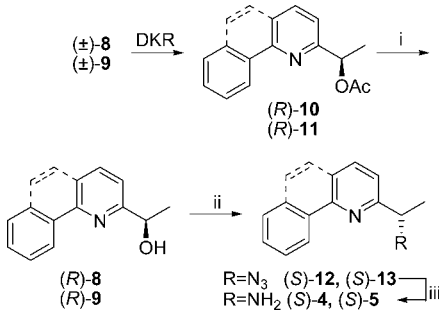
(16) (a) Paetzold, J; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 17620–17621. (b) Parvulescu, A.; De Vos, D.; Jacobs, P. *Chem. Commun.* **2005**, 5307–5309.

(17) Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169–1190.

(18) Uenishi, J.; Hiraoka, T.; Hata, S.; Nishiwaki, K.; Yonemitsu, O. *J. Org. Chem.* **1998**, *63*, 2481–2487.

(19) (a) Persson, B. A.; Larsson, A. L.; Le Ray, M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645–1650. (b) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **1997**, *36*, 1211–1212.

**SCHEME 2. Synthesis of Chiral Ligands (*S*)-4 and (*S*)-5**[a]



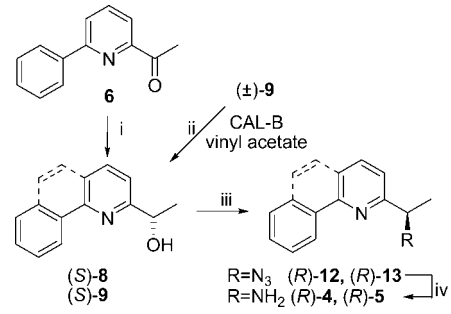

[a] (i) $K_2CO_3$, MeOH/$H_2O$, rt, 6 h, 100%. (ii) DPPA, DBU, toluene, 0 °C then at rt, 75%. (iii) $Ph_3P$, THF, $H_2O$, rt, 95%.

Hydrolysis under mild basic conditions of the optically active esters (*R*)-**10** and (*R*)-**11** gave the corresponding enantiopure secondary alcohols (*R*)-**8**[18] and (*R*)-**9**, in 70% overall yield from the racemic alcohols (Scheme 2). The (*R*) configuration of the compounds thus obtained results from the well-known preferential recognition of (*R*) enantiomers by CAL-B.[12] For the novel alcohol (*R*)-**9**, this configurational assignment was further supported by the CD spectra of the final amine products.[20] To obtain the target amines (*S*)-**4** and (*S*)-**5**, the homochiral alcohols (*R*)-**8** and (*R*)-**9** were first converted into the corresponding azides (*S*)-**12** and (*S*)-**13** (Scheme 2). This transformation was best carried out with diphenylphosphoroazidate (DPPA) in the presence of DBU.[21] These conditions led to a clean $S_N2$ inversion, avoiding racemization and olefin formation, which are commonly observed in the classical Mitsunobu reaction. By this procedure, alcohols (*R*)-**8** and (*R*)-**9**, having >99.9% ee and >99% ee respectively, were converted into the corresponding azides (*S*)-**12** and (*S*)-**13**, with only a slight erosion of the enantiomeric purity, which dropped to 95% in the case of (*S*)-**13**. Finally, conversion of the azides into the corresponding amines (*S*)-**4** (97% ee) and (*S*)-**5** (95% ee) was carried out by treatment with $Ph_3P$ in refluxing THF/$H_2O$[22] (Scheme 2).

The CD spectra of chiral ligands (*S*)-**4** and (*S*)-**5** thus obtained[20] support the configurational assignments; in particular, the sign of the Cotton effect for the band at around 280 nm is the same for both ligands, suggesting that they have the same configuration. The same, of course, must be true for all of their precursors; as the (*R*) configuration had already been attributed to the acetate **10** derived from the CAL-B catalyzed transesterification of racemic alcohol **8**,[18] the same configuration can also be attributed to the acetate **11** obtained from the kinetic resolution of **9**.

Having succeeded in synthesizing the enantiopure (*S*) ligands **4** and **5**, we then proceeded to the synthesis of the corresponding (*R*) enantiomers by a complementary biocatalytic approach. We anticipated from Prelog's rule[23] that the baker's yeast reduction of prochiral ketones **6** and **7** would proceed with delivery of the hydride to the Re face of the carbonyl, affording the (*S*) alcohols. Accordingly, when the reduction of **6** was carried out under fermenting conditions (37 °C, glucose, phosphate buffer, pH 7.4), 98% conversion was reached in 6 days, giving the expected alcohol (*S*)-**8** in >99.9% ee and 76% yield after purification (Scheme 3). Surprisingly, under the same conditions,

**SCHEME 3. Synthesis of Chiral Ligands (*R*)-4 and (*R*)-(5)**[a]




[a] (i) Baker's yeast, 37 °C, glucose, phosphate buffer, pH 7.4, 70%. (ii) See Table 1, entry 2. (iii) DPPA, DBU, 75%. (iv) $Ph_3P$, THF/$H_2O$, 95%.

the bioreduction of the tricyclic ketone **7** did not proceed beyond 5% conversion after 6 days. This lack of reactivity is a likely consequence of the steric hindrance of the rigid tricyclic aromatic structure that prevents the substrate from accessing the active site of the alcohol dehydrogenase. However, the desired alcohol (*S*)-**9** could be obtained by the classical kinetic resolution procedure (Table 1, entry 2); by stopping the acylation at 44% conversion, unreacted (*S*)-**9** was isolated in 47% yield and 86% ee. Conversion of the alcohols (*S*)-**8** and (*S*)-**9** thus obtained into the corresponding amines (*R*)-**4** and (*R*)-**5** was carried out by the two-step procedure already described. Thus, azides (*R*)-**12** (>99.9% ee) and (*R*)-**13** were obtained in 75% yield from the alcohols and DPPA and reduced with triphenylphosphine to give the desired products (Scheme 3) with >99.9% ee and 80% ee, respectively. The CD spectra of ligands (*R*)-**4** and (*R*)-**5** confirm the structural assignments.[20]

In conclusion, three novel chiral, nonracemic CNN pincer ligands (*S*)-**4** (49%, 97% ee), (*R*)-**5** (32%, 80% ee), and (*S*)-**5** (50%, 95% ee) have been synthesized from the corresponding ketones **6** and **7** by a combination of chemical and enzymatic methods. The same chemoenzymatic approach also allowed significant improvement in the synthesis of the known ligand (*R*)-**4**, which has been now obtained in 50% yield (from the ketone **6**) and 99.9% ee. In particular, we have demonstrated that the DKR of pyridyl ethanols is a superior method for the synthesis of chiral CNN pincer ligands, on account of the high enantioselectivity and wide substrate specificity of CAL-B.

Screening of the new ligands in the catalytic hydrogen transfer reduction and hydrogenation of prochiral ketones is underway and will be reported elsewhere.

## Experimental Section

**DKR of Racemic Alcohols 8 and 9.** Catalyst [$Ru_2(CO)_4(\mu$-H)($C_4Ph_4$-COHOC$C_4Ph_4$)] (0.044 mg, 0.04 mmol) and Novozyme 435 (60 mg) were suspended in toluene, under argon. A degassed solution of the racemic alcohol (2 mmol) and 4-chlorophenyl acetate (1.02 g, 6 mmol) in toluene (5 mL) was transferred to this suspension, and the mixture was stirred under argon, at 70 °C, for 46 h until complete conversion (GC). The enzyme was filtered off, and the reaction mixture was separated on silica (petroleum ether: ethyl acetate as eluant) to yield the acetates (*R*)-(+)-**10** and (*R*)-(+)-**11**.

**(*R*)-(+)-2-(1-Acetoxyethyl)-6-phenylpyridine ((*R*)-10).** (*R*)-**10** was obtained in >99.9% ee and 71% yield (93% conversion) from the DKR of alcohol **8**. $[\alpha]_D$ + 87.0 (*c* 0.25, $CHCl_3$) [lit.:[18] $[\alpha]_D$ + 86.0 (*c* 1.00, $CHCl_3$), ee 98%]. Spectroscopic data were in agreement with those reported.[18]

**(*R*)-(+)-2-(1-Acetoxyethyl)benzo[*h*]quinoline ((*R*)-11).** (*R*)-**11** was obtained in >99% ee and 73% yield (92% conversion) from the DKR of alcohol **9**. $[\alpha]_D$ + 119.0 (*c* 0.5, $CHCl_3$).

(20) See Supporting Information.
(21) Thomson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886–5888.
(22) Horner, L.; Gross, A. *Liebigs Ann. Chem.* **1955**, *591*, 117–134.
(23) Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119–122.

**(*R*)-(−)-2-(1-Hydroxyethyl)-6-phenylpyridine ((*R*)-8).** The acetate (*R*)-**10** (1.4 mmol) was hydrolyzed with $K_2CO_3$ (193 mg, 1.4 mmol) in methanol/water (1:1) for 6 h at room temperature. Methanol was evaporated under reduced pressure, and the aqueous phase was extracted with $CHCl_3$ (3 × 20 mL). The combined organic phases were extracted with brine, dried over $Na_2SO_4$, and concentrated in vacuo. Chromatography on silica gave the alcohol (*R*)-(−)-**8** (100%, >99.9% ee, by chiral HRGC); $[\alpha]_D$ − 24.0 (*c* 0.30, $CHCl_3$).

**(*R*)-(−)-2-(1-Hydroxyethyl)benzo[*h*]quinoline ((*R*)-9).** (*R*)-**9** was obtained quantitatively from the hydrolysis of acetate (*R*)-**11**, as described for (*R*)-**10**; ee >99% (from the $^1$H NMR analysis of the corresponding Mosher's ester), $[\alpha]_D$ − 85.3 (*c* 0.3, $CHCl_3$).

**Baker's Yeast Reduction of 6: (*S*)-(+)-2-(1-Hydroxyethyl)-6-phenylpyridine ((*S*)-8).** Glucose (112 g) was added to a stirred suspension of dry baker's yeast (56 g) in phosphate buffer (0.1 M, pH 7.4). The mixture was preincubated for 30 min at 37 °C, and the ketone **6** (0.7 g, 3.6 mmol) was added at room temperature. The reaction was monitored by HRGC, and after 6 days the broth was extracted with ether. The organic phase was dried and evaporated to give a residue which was chromatographed on an $SiO_2$ column giving (*S*)-**8**. 76% yield at 98% conv.; ee >99.9% (by HRGC). $[\alpha]_D$ + 22.0 (*c* 0.55, $CHCl_3$) [lit.:[18] $[\alpha]_D$ + 28.0 (*c* 1.00, $CHCl_3$), 99% ee]. Spectroscopic data were in agreement with those reported.[18]

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**Supporting Information Available:** Full experimental procedures and spectral and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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