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Optically active phenanthrolines in asymmetric catalysis

II *. Enantioselective transfer hydrogenation of acetophenone by rhodium / alkyl phenanthroline catalysts

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Abstract

Three new alkyl phenanthrolines containing a norpinanyl substituent as the common chiral target, have been synthesized and tested as ligands in the rhodium-catalyzed asymmetric transfer hydrogenation of acetophenone. A marked catalytic activity was observed, but the highest optical yield was 24% e.e.

Introduction

In recent years our research efforts in the field of asymmetric catalysis have been mainly directed towards the synthesis of optically active pyridine derivatives to be used as chiral ligands in enantioselective processes promoted by transition metal complexes. This approach stems from the consideration that chiral nitrogen ligands are usually cheaper, easier to prepare and to recover, more chemically resistant than optically active diphosphines, and can be profitably employed in many asymmetric processes [1].

In an earlier paper on this subject we demonstrated that the alkyl-2,2′-bipyridines (**2a–2e**) (Fig. 2) are efficient chiral ligands in the rhodium-catalyzed asymmetric

* For part I see Ref. 4.

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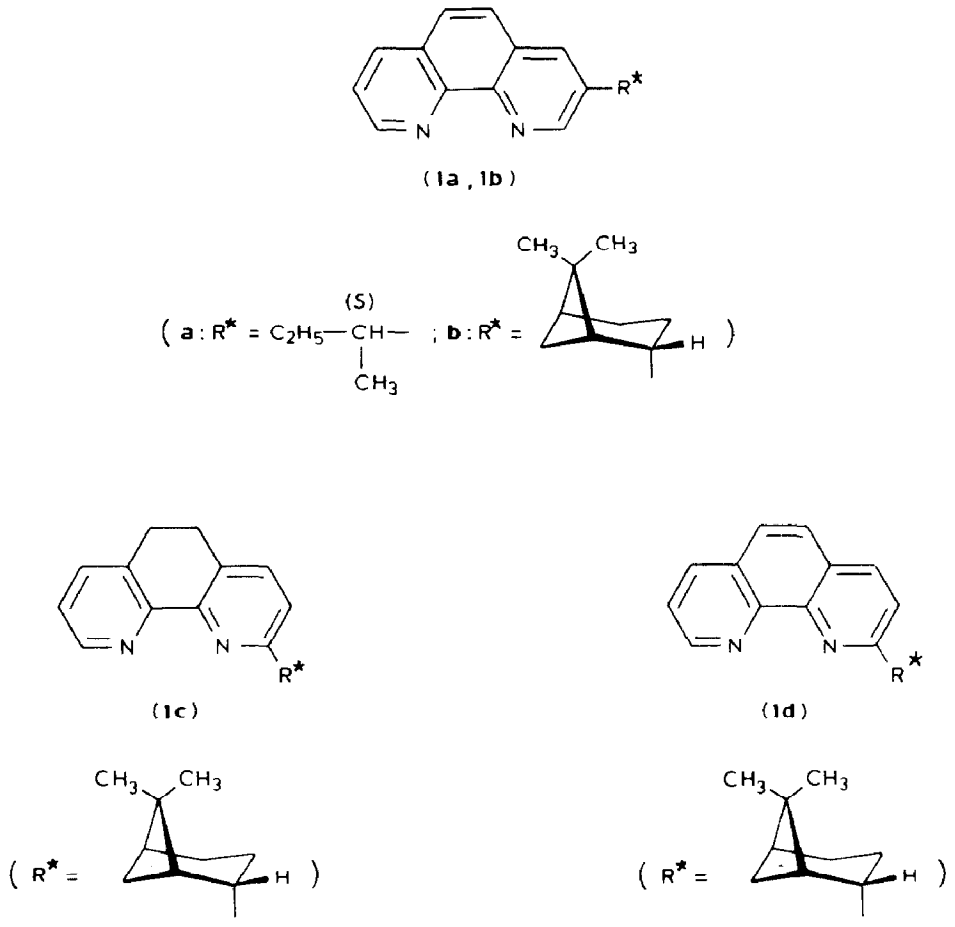


Fig. 1. Chiral alkylphenanthrolines.

transfer hydrogenation of acetophenone [2]. The stereoselectivity of the reaction increased, from 2.5% e.e. with **2d** to 7.5% e.e. with **2a**, as the substituent was moved closer to the coordination center, and attained the highest value (15% e.e.) when a chiral alkyl group of increasing complexity, such as that in **2c**, was present on the carbon atom adjacent to the nitrogen.

Further work aimed at improving the enantio-differentiating ability of the nitrogen ligands, revealed that the presence on the bipyridine ring of a more demanding alkyl substituent, as in the case of conformationally rigid tetrahydroquinoline **2f** derived from (+)-camphor [3], affected unfavourably both the rate and the stereoselectivity of the process. In contrast, stiffening the heterocyclic framework of the ligand resulted in a remarkable enhancement of the asymmetric bias: 3-s-butyl-1,10-phenanthroline (**1a**) (Fig. 1) is at least one order of magnitude more efficient that the structurally related 5-s-butyl-2,2′-bipyridine (**2d**) (31% e.e. vs. 2.5% e.e.) [4].

As these results called for a deeper investigation of the scope of chiral phenanthrolines in the rhodium-catalyzed transfer hydrogenation of prochiral ketones, the preparation of new representatives of this class of ligands was undertaken.

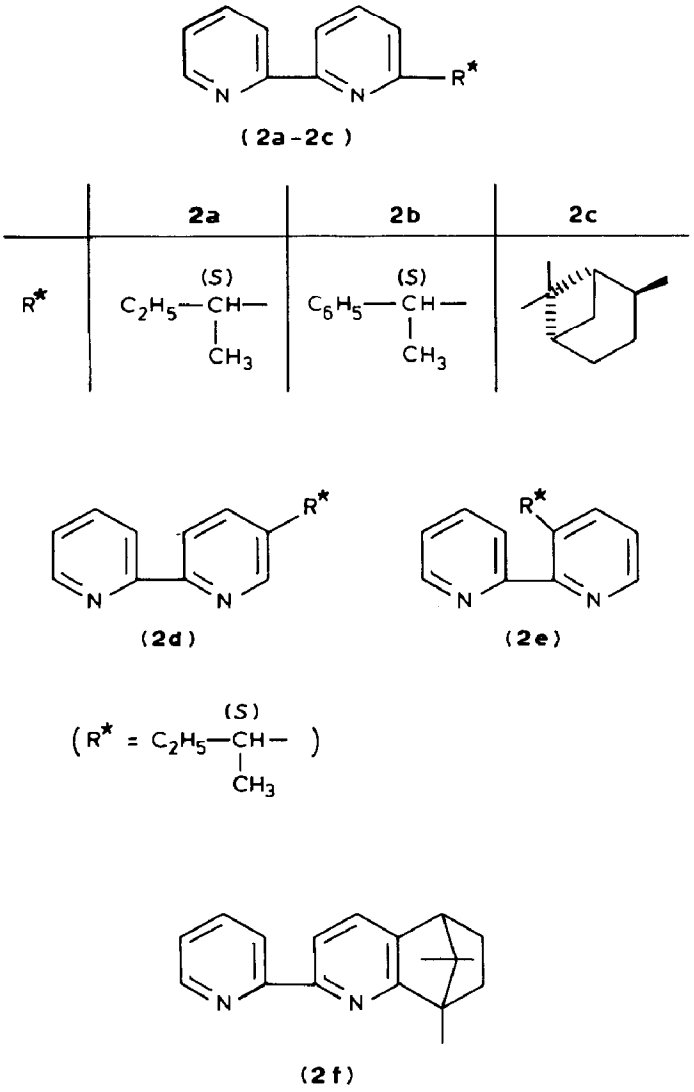


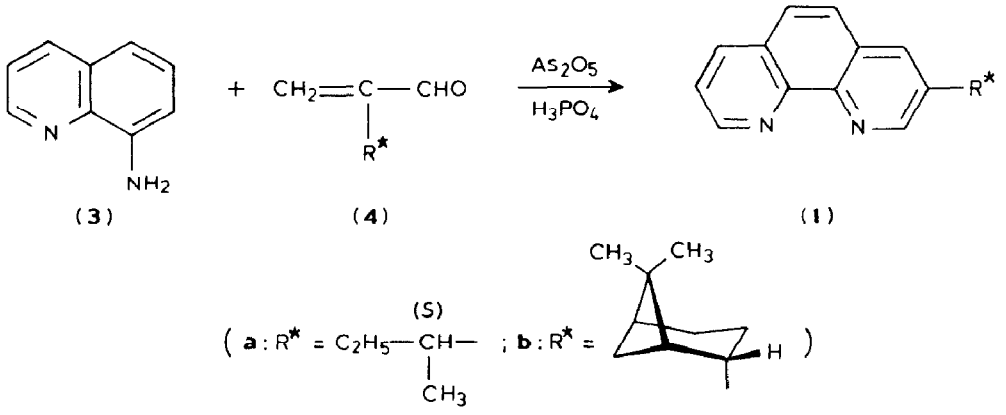
Fig. 2. Chiral alkylbipyridines.

In this paper we describe the synthesis of alkylphenanthrolines **1b–1d** and their use in the asymmetric transfer hydrogenation of acetophenone. A preliminary report on this subject has appeared [5].

Results and discussion

Synthesis of the chiral ligands

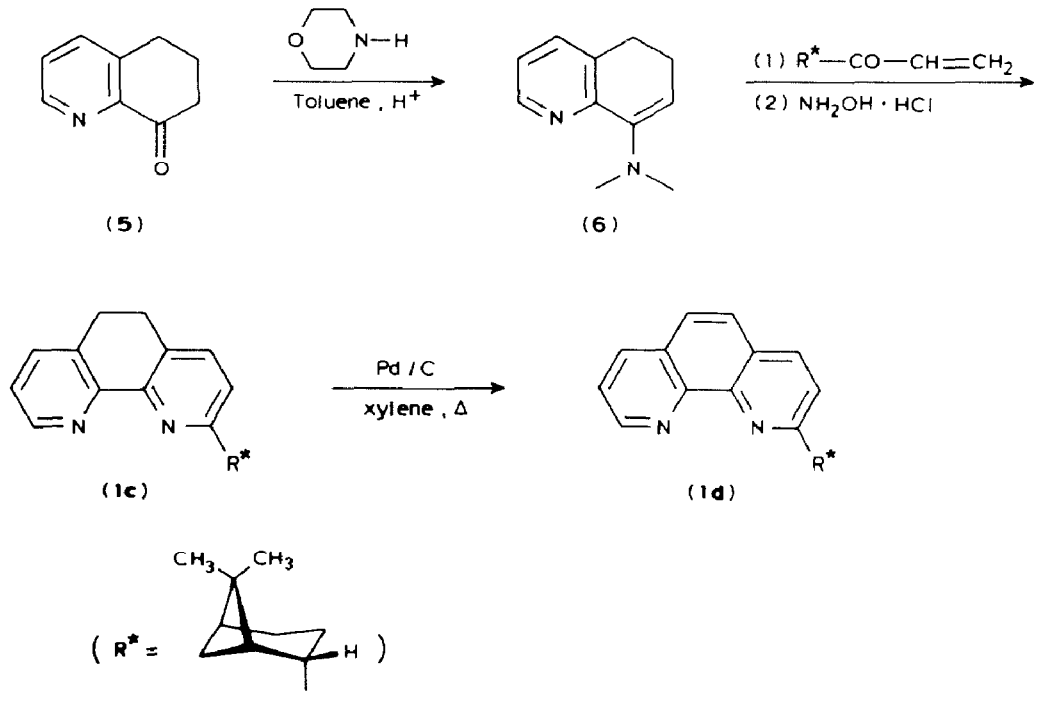
The choice of the (1*S*,2*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-yl (norpinanyl) group as the common chiral target for the new phenanthrolines **1b–1d** was based on the ready availability of suitable chiral precursors for their preparation and on the possibility of a direct comparison of its efficiency with that of the corresponding 2,2′-bipyridine (**2c**). According to the procedure previously employed for the s-butyl analogue, commercial 8-aminoquinoline **3** was heated for 3 h with 2-



Scheme 1.

norpinanylacrolein (**4b**) in 85% phosphoric acid in the presence of arsenic acid to give the ligand **1b** (Scheme 1). Pure **1b** was recovered in 40% yield as pale yellow crystals after chromatography on silica gel and displayed analytical and spectroscopic data consistent with the expected structure. The same optical purity of the original chiral precursor *trans*-myrtanol could be confidently assumed for **1b** since the overall synthetic sequence has been previously demonstrated to involve no racemization [4,6].

For the preparation of 5,6-dihydrophenanthroline derivative **1c**, the morpholino enamine **6** of readily available 5,6-dihydro-8(7*H*)-quinolinone (**5**) [7] was treated with norpinanyl vinyl ketone and the crude product was cyclized by reaction with a



Scheme 2.

Table 1

Reduction of acetophenone by hydrogen transfer from 2-propanol catalyzed by $[Rh(cod)Cl]_2$ and chiral alkyl 1,10-phenanthrolines (Reaction conditions: 2.5×10^{-5} mol $[Rh(cod)Cl]_2$ in 45 ml of 2-propanol; [substrate]/[KOH]/[Rh] = 200/10/1; T 83° C)

Ligand	[Ligand]/[Rh]	TN [a]	Optical yield [b]
1b	2	510	20.5
1b	5	255	17.0
1b	10	210	24.0
1b	25	174	18.5
1b	5	91	11.2 [c]
1b	5	200	20.4 [d]
1b	5	24	16.0 [e]
1c	5	344	14.0
1c	10	509	14.0
1c	25	360	9.4
1d	1	15	14.3
1d	2	45	15.4
1d	5	180	12.0
1d	10	225	10.5
1d	25	186	7.3

[a] TN (turnover number): moles of substrate converted per hour and g-atom of rhodium. [b] In all the experiments the prevailing enantiomer had the (R) configuration. [c] Substrate to metal ratio = 1000. [d] Substrate to metal ratio 100. [e] Reaction temperature 45° C.

two fold excess of hydroxylamine hydrochloride in acetic acid (Scheme 2). Pure compound **1c** was isolated in 43% yield as a viscous oil by column chromatography. Conversion of **1c** into **1d** in high yield was readily accomplished by dehydrogenating the dihydro derivative in refluxing xylene in the presence of a catalytic amount of palladium on charcoal.

The diasteromeric purity of compounds **1c** and **1d** could not be directly checked by GLC, as it could in the case of the corresponding bipyridine derivative **2c** [2]. Taking into account, however, that both the ligands **1c** and **2c** arise from the identical chiral precursor through the same synthetic procedure, it seems reasonable to assume that they have comparable diastereomeric compositions.

Transfer hydrogenation experiments

The catalytic runs were carried out under conditions strictly comparable with those previously employed for the same process. Whatever the ligand tested, active catalytic solutions were always obtained following the usual preactivation procedure [2]. The experimental parameters and the results obtained in the transfer hydrogenation of acetophenone with rhodium catalysts prepared in situ from $[Rh(cod)Cl]_2$ and the chiral phenanthrolines **1b**, **1c** and **1d** are reported in Table 1.

The rate of the process was quite dependent on the structure and the concentration of the ligand, the dihydrophenanthroline **1c** giving rise to the most active catalytic species. With the 2-alkyl-substituted derivatives **1c** and **1d**, the reaction rate increased as the ligand to metal ratio was increased up to 10/1, and then decreased upon further increase in the ratio. In contrast, the rate fell steadily when the ratio of the 3-substituted phenanthroline **1b** to the rhodium was increased from 2 to 25. The same behaviour was previously observed with 3-s-butylphenanthroline (**1a**) [4].

Following the preactivation treatment, the 3-substituted phenanthrolines gave rise to deep blue-green catalytic solutions, whereas the 2-substituted derivatives gave brown-black solutions. In the latter case, a reduced homogeneity of the active catalytic system, evidenced by the separation of a black precipitate during the preactivation, was noticed in the experiments carried out at ligand to metal ratios equal to or less than 5. Although we have previously demonstrated that the solid separated, confidently identified as rhodium metal, is devoid of any catalytic activity and does not affect the reliability of the results [3], in these runs the actual concentration of the active catalyst is obviously lower than expected. This may largely account for the observed dependence of the reaction rate on the concentration of 2-substituted ligands **1c** and **1d**.

In contrast, the catalytic solutions obtained with 3-norpinanylphenanthroline (**1b**) were strictly homogeneous over the whole concentration range explored, and the observed rate dependence is indicative of the presence of a dissociative step in the catalytic cycle or of a competition between the substrate and the ligand.

No significant relationship could be found between the extent of the asymmetric induction and the ligand concentration or the reaction rate. The highest optical yield recorded during this work (24% e.e.) was far from the highest values obtained in the transfer hydrogenation of phenyl alkyl ketones either with rhodium (75% e.e.) [8] or with iridium (80% e.e.) [9] catalysts, and was also lower than the best one previously observed by us [4]. It could not be improved by lowering the reaction temperature, and rather surprisingly, it was obtained only with the 3-substituted phenanthroline **1b**, and not with the 2-substituted derivatives **1c** or **1d** as we expected.

These last compounds displayed almost identical stereo-differentiating efficiencies and showed no improvement over the corresponding bipyridine **2c**. This contrasts with the behaviour displayed by the 3-s-butyl derivatives **1a** and **2d** and with the sharp differences in the activities of the relevant catalysts formed from **1b**, **1c** and **2c**.

For ease of comparison, the results recorded in the asymmetric transfer hydrogenation of acetophenone catalyzed by rhodium/chiral bipyridines **2** and phenanthrolines **1** listed in Fig. 1 and 2 are summarized in Table 2.

Table 2

Turnover rates (optical yields) recorded in the rhodium catalyzed asymmetric transfer hydrogenation of acetophenone with pyridine derived ligands (Reaction conditions: 2.5×10^{-5} mol $[Rh(cod)Cl]_2$ in 45 ml of 2-propanol; [substrate]/[KOH]/[Rh] = 200/10/1; T 83° C).

Ligand	[Ligand]/[Rh] molar ratio			
	2	5	10	25
1a	360 (25.5)	144 (20.5) [a]	88 (17.2)	45 (10)
1b	510 (20.5)	255 (17.0)	210 (24.0)	174 (18.5)
1c	–	344 (14.0)	509 (14.0)	360 (9.3)
1d	45 (15.4)	180 (12.0)	225 (10.0)	186 (7.3)
2a	28 (2.7)	67 (7.2)	172 (4.5) [b]	–
2b	43 (1.8)	40 (4.3)	82 (2.5)	–
2c	–	85 (14.8)	52 (1.3)	–
2d	48 (2.5)	29 (1.6)	34 (1.7)	–
2f	42 (9.4)	37 (1.4)	107 (1.4)	142 (0.5)

[a] [Ligand]/[Rh] molar ratio = 4. [b] [Ligand]/[Rh] molar ratio = 15.

As can be seen, the reaction rates recorded with phenanthroline-based catalysts are always higher than those involving bipyridines. The same is true for the stereoselectivity, with the noticeable exception of 2-substituted derivatives, for which the top optical yields were almost identical for both classes of ligands.

The data also reveal that the outcome of the reaction depends heavily on the position as well as on the structure of the substituent in the chiral alkyl phenanthrolines. Although not so obvious, the trend is the same as for bipyridine-based ligands the behaviour of 2-substituted derivatives closely resembling that of the corresponding phenanthroline derivatives.

The questions which are not easy to answer in the case of phenanthroline ligands are (i) why the more remote substituent can transfer the chiral information more efficiently (see **1b** vs. **1c** and **1d**), and (ii) why the simpler chiral group does this better than the more complex one (see **1a** vs. **1b**). While the second question is a matter only for speculation, the first can be tentatively answered.

In the case of 3-substituted phenanthrolines, the close analogies with the behaviour of 1,10-phenanthroline based catalysts seem to indicate that, in accord with the suggestions of Mestroni and coworkers [10], the main catalytic species active in our concentration range must be a mononuclear rhodium(I) derivative containing two moles of coordinated ligand.

Earlier [3] and present findings indicate that coordination to rhodium of 2-substituted derivatives is strongly affected by the presence of an alkyl substituent on the adjacent carbon. The steric constraints involved can greatly affect the equilibria leading to the active catalyst, as is particularly evident for ligands possessing a rigid framework, such as **1c**, **1d** and **2f** (Table 2). Furthermore, the formation of cyclometallated rhodium complexes, like those obtained from **2b** with platinum(II) and palladium(II) salts, cannot be excluded [11]. It is possible that the 2-substituted phenanthrolines may give rise to more than one catalytically active species, and we suspect that the low stereoselectivity is the consequence of a delicate balance between the concentration and the activity of the various rhodium complexes involved in the process.

Conclusions

The rhodium catalysts obtained from the new phenanthrolines **1b–1d** display only fair stereoselectivities in the transfer hydrogenation of acetophenone. Despite this, the high catalytic activities observed confirm that this type of ligand is better than bipyridines for applications in homogeneous catalysis.

The pronounced ability of the sp^2-nitrogen to coordinate and the remarkable stability of the heterocyclic nucleus suggest that their use should be extended to other transition metal-catalyzed processes, in which a deeper knowledge of the intimate reaction mechanism should facilitate the choice of the best structure for the ligand.

Experimental

Materials

Isopropanol and acetophenone were distilled before use and stored under nitrogen. (−)-(*S*)-2-Methyl-1-butanol, $[\alpha]_{546}^{25}$ −6.3 (c = 10; ethanol), (−)-*trans*-myrtanol,

$[\alpha]_D^{20}$ −29.2 (neat) and 8-aminoquinoline were purchased (Fluka AG) and used as received. 2-s-Butylacrolein and 2-norpinanylacrolein (**4**) were prepared from 2-methylbutanol and *trans*-myrtanol respectively, by a published method [6]. Chloro(1,5-cyclooctadiene)rhodium(I) dimer [12] and 5,6-dihydro-8(7*H*)-quinolinone (**5**) [7] were prepared as previously described.

General procedures

Melting points were determined on a Büchi melting point apparatus and are uncorrected. GLC analyses were performed on a Perkin–Elmer 3920B instrument fitted with a 10 ft packed column of 10% SP-1000 on Supelcoport 80–100. ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer in deuterochloroform solution with tetramethylsilane as internal standard ($\delta = 0$). Optical rotations were determined with a Perkin–Elmer 241 polarimeter. Elemental analyses were performed with a Perkin–Elmer Elemental Analyzer 240B.

*(+)-(S)-3-s-Butyl-1,10-phenanthroline (**1a**)*

To a mixture of 8-aminoquinoline (5 g, 35 mmol), 85% phosphoric acid (35 ml) and 80% arsenic acid (6.4 ml) kept at 100° was slowly added (+)-(*S*)-s-butylacrolein (7.8 g, 70 mmol). The mixture was kept at 115°C for 2 h then poured onto ice. After extraction with ether, the aqueous phase was made alkaline with 10% NaOH and extracted again with ether. The crude product recovered after removal of the solvent was chromatographed on a short column of silica gel (50 g) with benzene as the eluant. Crystallization from 1/1 benzene/hexane afforded pure **1a**: 2.5 g (30% yield); m.p. 91–93°C; $[\alpha]_D^{25}$ +22.4 ($c = 1.04$; ethanol). ^{1}H NMR: 9.05 (dd, 1H, 9H); 8.95 (d, 1H, 2H); 8.07 (dd, 1H, 7H); 7.87 (d, 1H, 4H); 7.63 (m, 2H, 5H and 6H); 7.43 (dd, 1H, 8H); 2.88 (m, 1H); 2.02–1.47 (m, 2H); 1.37 (d, 3H); 0.87 (t, 3H). Found: C, 81.54; H, 6.55; N, 11.61. $C_{16}H_{16}N_2$ calc.: C, 81.37; H, 6.81; N, 11.82%.

*(+)-3-{(1S,2S)-6,6-Dimethylbicyclo[3.1.1]hept-2-yl}-1,10-phenanthroline (**1b**)*

The procedure described above, starting from 3.74 g (26 mmol) of 8-aminoquinoline and 5 g (28.6 mmol) of 2-norpinanylacrolein, gave pure **1b** (3.2 g; 41%; after column chromatography (benzene) and recrystallization (benzene/hexane)): m.p. 173°C; $[\alpha]_D^{25}$ +28.1 ($c = 2.0$; ethanol). ^{1}H NMR: 9.06 (dd, 1H, 9H); 8.98 (d, 1H, 2H); 8.07 (dd, 1H, 7H); 7.90 (d, 1H, 4H); 7.62 (m, 2H, 5H and 6H); 7.43 (dd, 1H, 8H); 3.67–3.27 (m, 1H); 2.45–1.66 (m, 8H); 1.13 (s, 3H); 1.00 (s, 3H). Found: C, 83.18; H, 7.16; N, 9.04. $C_{21}H_{22}N_2$ calc.: C, 83.41; H, 7.33; N, 9.26%.

*Morpholino enamine of 5,6-dihydro-8(7H)-quinolinone (**6**)*

A solution of 5,6-dihydro-8(7-*H*)-quinolinone (**5**) (1.9 g; 12.9 mmol) in anhydrous benzene (50 ml) containing morpholine (5.6 g; 65 mmol) and *p*-toluenesulfonic acid (0.2 g), was refluxed in a Kumagawa apparatus containing 4A molecular sieves (5 g). After 24 h the solvent was removed and the residue was distilled under reduced pressure. Recrystallization of the distillate (benzene/hexane 1/4) afforded pure **6**: 2.27 g (81%); m.p. 86–87°C. ^{1}H NMR: 8.43–8.23 (m, 1H, 2H); 7.43–6.80 (m, 2H, 3H and 4H); 5.40 (t, 1H, 7H); 4.00–3.73 (m, 4H); 3.06–2.57 (m, 8H). Found: C, 72.47; H, 7.21; N, 12.88. $C_{13}H_{16}N_2O$ calc.: C, 72.19; H, 7.46; N, 12.95%.

*(−)-2-{(1S,2S)-6,6-Dimethyl[3.1.1]hept-2-yl}-5,6-dihydro-1,10-phenanthroline (**1c**)*

A solution of the enamine **6** (2.2 g; 10.2 mmol) and norpinanyl vinyl ketone [2] in anhydrous benzene (25 ml) was refluxed for 70 h. After removal of the solvent the residue was dissolved in acetic acid, hydroxylamine hydrochloride was added, and the resulting solution was kept for 5 h at 115°C. Most of the solvent was then removed under reduced pressure, water (30 ml) was added, and the mixture was extracted with ether. The aqueous layer was separated, made alkaline with 10% NaOH, and extracted again with ether. After drying (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on neutral alumina (150 g). Elution with ether and distillation afforded pure **1c** as a viscous oil: 1.3 g (43%); b.p. 200°C at 0.05 torr; $[\alpha]_D^{25}$ −3.87 ($c = 2.2$; abs. ethanol). ^{1}H NMR: 8.57 (dd, 1H, 9H); 7.57–6.83 (m, 4H); 3.83–3.40 (m, 1H); 2.82 (s, 4H); 2.40–1.50 (m, 8H); 1.12 (s, 3H); 0.98 (s, 3H). Found: C, 83.24; H, 7.68; N, 8.95. $C_{21}H_{24}N_2$ calc.: C, 82.86; H, 7.94; N, 9.20%.

*(+)2-{(1S,2S)-6,6-Dimethylbicyclo[3.1.1]hept-2-yl}-1,10-phenanthroline (**1d**)*

A suspension of 10% palladium on charcoal (0.5 g) in xylene (20 ml) containing **1c** (1.2 g; 4 mmol) was refluxed for 4 h. After cooling, the suspension was filtered and the solvent was removed. The residue was chromatographed on neutral alumina (60 g) with ether as the eluant. The ligand **1d** was obtained in pure form as a light yellow viscous oil: 1.1 g (90%); $[\alpha]_D^{25}$ +4.36 ($c = 2.01$; abs. ethanol). ^{1}H NMR: 9.23–9.06 (m, 1H, 9H); 8.23–7.96 (m, 2H, 4H and 7H); 7.70–7.27 (m, 4H); 4.16–3.76 (m, 1H); 2.50–1.70 (m, 8H); 1.30 (s, 3H); 1.06 (s, 3H). Found: C, 83.58; H, 7.17; N, 8.94. $C_{21}H_{22}N_2$ calc.: C, 83.41; H, 7.33; N, 9.26%.

Catalytic transfer hydrogenation of acetophenone

The catalyst was prepared in situ by adding the appropriate amount of the phenanthroline **1** to a solution of $[Rh(cod)Cl]_2$ (2.5×10^{-5} mol) in 2-propanol (40 ml) under nitrogen. After addition of KOH (5×10^{-4} mol) in 5 ml of 2-propanol, the solution was refluxed for 1 h and then stirred overnight at room temperature before the addition of acetophenone. The progress of the reaction was monitored by GLC (10% SP-1000 on 80/100 Supelcoport; 3 m × 3 mm; 170°C). At the end of the reaction, the solution was neutralized (AcOH) and the solvent was evaporated. The product was then recovered by distillation under reduced pressure. The optical purity of the carbinol was determined in methanol solution ($c = 5$) by use of the value $[\alpha]_D^{23}$ of −45.5 for the pure S enantiomer [13].

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