Applied Organometallic Chemistry (1988) 2 227–231

0268-2605/88/02303227/$03.50

Optically active alkylbipyridines as chiral ligands in asymmetric catalysis. Synthesis of 2-(2′-pyridyl)-5,6,7,8-tetrahydro-8,9,9-trimethyl-5,8-methanoquinoline and rhodium-promoted asymmetric transfer hydrogenation of acetophenone

Serafino Gladiali,*† Giorgio Chelucci*, Franco Soccolini* and Giovanna Delogu‡
*Dipartimento di Chimica, Universitá di Sassari, Via Vienna 2, 07100 Sassari, Italy and ‡C.N.R. – Istituto per l'Applicazione delle Tecniche Chimiche Avanzate ai Problemi Agrobiologici, Via Vienna 2, 07100 Sassari, Italy

Received 27 January 1988 *Accepted 24 February 1988*

The title compound, a new chiral alkyl 2,2′-bipyridine containing a rigid alkyl framework, can be prepared through a six-step reaction sequence from (+)-camphor. Coordination of the new ligand to rhodium(I) procatalysts occurs with difficulty and the resulting species display a very low stereoselectivity in the catalytic transfer hydrogenation of acetophenone.

Keywords: Chiral rhodium catalysts, asymmetric transfer hydrogenation, optically active alkylbipyridines

INTRODUCTION

In recent years a great deal of our research efforts have been concerned with the synthesis of optically active nitrogen heterocycles that could act as chiral ligands for transition metal ions in homogeneously catalyzed reactions and with the search for asymmetric processes where these ligands could be profitably employed.

The first achievements of this work, for which a patent was also filed,[1] have been the synthesis of a representative set of optically active alkyl 2,2′-bipyridines,[2,3] a new class of chiral chelating nitrogen ligands, and the asymmetric transfer hydrogenation of acetophenone by means of rhodium catalysts with these new chiral modifiers.[4] This last achievement has a meaning that goes beyond the absolute values of the optical inductions recorded; these, on the whole, are quite low (maximum optical purity 15%). This result demonstrates the soundness of the initial ideas that moved this investigation, i.e. that nitrogen derivatives based on the pyridine framework could be chiral modifiers for transition metal ions as efficient as tertiary alkyl phosphines, with the advantage that the nitrogen ligands are more stable than phosphines and can be easily recovered at the end of the process by a simple acid–base work-up.

This last feature, which has been precisely checked,[4] broadens the potential of the new class of ligands because it acts as a multiplying factor of their catalytic ability.

Following these results, our next goal was to increase the enantiodifferentiating capability of the nitrogen derivatives by preparing suitable modifications of the basic structure that could provide a more rigid array of the ligands around the metal center. To this purpose, two alternative routes were considered: the first was to enhance the rigidity of the alkyl substituent, leaving untouched the 2,2′-bipyridine matrix; the second was to stiffen the heterocyclic framework.

Both these possibilities have been explored and, in keeping with the latter one, our most recent contribution in this field reports the synthesis of 3-*sec*-butyl-1,10-phenanthroline and its utilization as a chiral modifier for rhodium in the asymmetric transfer hydrogenation of acetophenone.[5] The maximum optical yield recorded in this case (31%) is twice as high as the best obtained with bipyridines and, more important, 12 times higher than the best stereoselectivity obtained in the same process with the structurally

†Author to whom correspondence should be addressed.

related 5-*sec*-butyl bipyridine.[5] Noticeably, the chirality of the reaction is reversed.

Work along the first strategy has been addressed towards the binding of the bornane skeleton to the bipyridine framework, using (+)-camphor as the starting chiron.

This paper reports the results obtained from this approach.

EXPERIMENTAL

Solvents and reagents were commercial products and were used after standard purification.

(+)-5,6,7,8-Tetrahydro-8,9,9-trimethyl-5,6-methanoquinoline, $[\alpha]^{25}$ + 36.8 (c = 2.103; cyclohexane) was prepared as described[6] from (+)-camphor, Fluka product, $[\alpha]^{25}$ + 43.5 (c = 10; EtOH).

(η-Cyclopentadienyl)cobalt-1,5-cyclo-octadiene was prepared according to the procedure reported by Bonnemann and co-workers.[7]

General methods

Melting points are uncorrected. GC measurements were carried out on a Perkin–Elmer 3920 instrument using a 6 ft packed column of 5% SE-30 on Chromosorb W80-100. Proton magnetic resonance spectra were recorded in deuterochloroform solution on a Varian T-60 spectrometer; values are given downfield from internal TMS. IR spectra were obtained with a Perkin–Elmer 983 instrument. Mass spectra were recorded with a Finningan 1020 GS/MS spectrometer. Optical rotations were determined with a Perkin–Elmer 141 polarimeter. Elemental analyses were performed with a Perkin–Elmer Elemental Analyzer 240 B.

Synthesis of 5,6,7,8-tetrahydro-8,9,9-trimethyl-5,8-methanoquinoline *N*-oxide (2)

A solution of 3-chloroperbenzoic acid (5.1 g, 30 mmol) in $CHCl_3$ (70 cm^3) was slowly added to a solution of (+)-5,6,7,8-tetrahydro-8,9,9-trimethyl-5,8-methanoquinoline **1** (4.2 g, 22.5 mmol) in $CHCl_3$ (30 cm^3).

The mixture was then stirred at room temperature for 7 h, and subsequently treated with 10% K_2CO_3 (50 cm^3). The organic layer was separated and the aqueous phase was extracted with $CHCl_3$ (3 × 25 cm^3). The combined organic extracts were dried over sodium sulfate and the solvent was evaporated. The solid residue was repeatedly washed with pentane to give the *N*-oxide **2** as white crystals (4.2 g, 92%), m.p. 134–135 °C.

Analysis: Calcd for $C_{13}H_{17}NO$ (203.37): C, 76.81; H, 8.43; N, 6.89. Found: C, 76.62; H, 8.80; N, 6.57%.

^{1}H-NMR (60 MHz): 7.85 (m, 1H, 2-H); 7.02 (m, 2H, 3- and 4-H); 2.80 (m, 1H, 5-H); 1.70 (s, 3H, $-CH_3$); 0.96 (s, 3H, $-CH_3$); 0.70 (s, 3H, $-CH_3$).

Synthesis of (+)-2-cyano-5,6,7,8-tetrahydro-8,9,9-trimethyl-5,8-methanoquinoline (3a)

A mixture of **2** (4.2 g, 20 mmol) and dimethyl sulfate (3 g, 20 mmol) was stirred at 85 °C for 3 h. After cooling, the crude *N*-methoxypyridinium methylsulfate was taken up with water (15 cm^3) and the solution was slowly added with stirring to aqueous potassium cyanide (3.1 g in 12 cm^3) at 0 °C.

The mixture was stirred overnight at room temperature and then was extracted with ether. The ethereal phase was washed with 10% hydrochloric acid (3 × 10 cm^3), dried with sodium sulfate and the solvent removed. The oily residue was distilled *in vacuo* to give **3a** (1.53 g; 35%), 98% pure by GC (180 °C), b.p. 120 °C/10 Pa.

IR (nujol): 2212 cm^{-1} (—CN). ^{1}H-NMR (60 MHz): 7.27 (m, 2H, 3- and 4-H); 2.86 (m, 1H, 5-H); 1.28 (s, 3H, $-CH_3$); 1.02 (s, 3H, $-CH_3$); 0.85 (s, 3H, $-CH_3$). MS (70 eV) *m/z* (%; fragment): 212 (36; M^+); 197 (31; M^+-CH_3); 169 (100; 197 − $CH_2=CH_2$); 155 (31). $[\alpha]^{25}$ +25.3 (c = 2.01; cyclohexane).

Processing the acid extracts by the same method afforded 1.1 g of the 4-cyano isomer **3b**.

MS (70 eV) *m/z* (%; fragment): 212 (26; M^+); 197 (21; $M^+ - CH_3$); 169 (100; 197 − $CH_2=CH_2$); 155 (21).

Synthesis of (−)-2-(2′-pyridyl)-5,6,7,8-tetrahydro-8,9,9-trimethyl-5,8-methanoquinoline 4

A solution of **3a** (1.53 g, 7.2 mmol) and (η-cyclopentadienyl)cobalt-1,5-cyclo-octadiene (0.2 g) in degassed toluene (25 cm^3) was introduction by suction into a 200 cm^3 autoclave from which the air had been evacuated (10 Pa). The reaction vessel was pressurized at 1.2 MPa with acetylene and then heated at 130 °C. The theoretical amount of acetylene (2 moles per mole of **3a**) was taken up within 10 h. After cooling and release of the residual gas, the suspension was filtered and the filtrate extracted with 10% hydrochloric acid. The aqueous phase was made alkaline with a 10% solution of sodium hydroxide and extracted with ether. Drying over sodium sulfate and

distillation afforded pure **4** (1.3 g, 69%), more than 99% pure on GC (200 °C): b.p. 135 °C/10 Pa.

Analysis: calcd. for $C_{18}H_{20}N_2$ (264.37): C, 81.78; H, 7.62; N, 10.60. Found: C, 81.54; H, 7.82; N, 10.35%.

^{1}H-NMR (60 MHz): 8.53–8.27 (m, 2H, 6′- and 3′-H); 8.06 (d, 1H, 4-H, J = 7 Hz); 7.60 (dt, 1H, 4′-H); 7.30 (d, 1H, 3-H, J = 7 Hz); 7.17–6.87 (m, 1H, 5′-H); 2.80 (m, 1H, 5-H); 1.37 (s, 3H, $-CH_3$); 1.02 (s, 3H, $-CH_3$); 0.60 (s, 3H, $-CH_3$).

MS (70 eV) m/z (%; fragment): 264 (34; M^+); 249 (41, $M^+ - CH_3$); 235 (22; $M^+ - CH_3, - CH_2$); 221 (100; $M^+ - CH_3, - CH_2{=}CH_2$). $[\alpha]^{25}$ −26.6 (c = 2.0; cyclohexane).

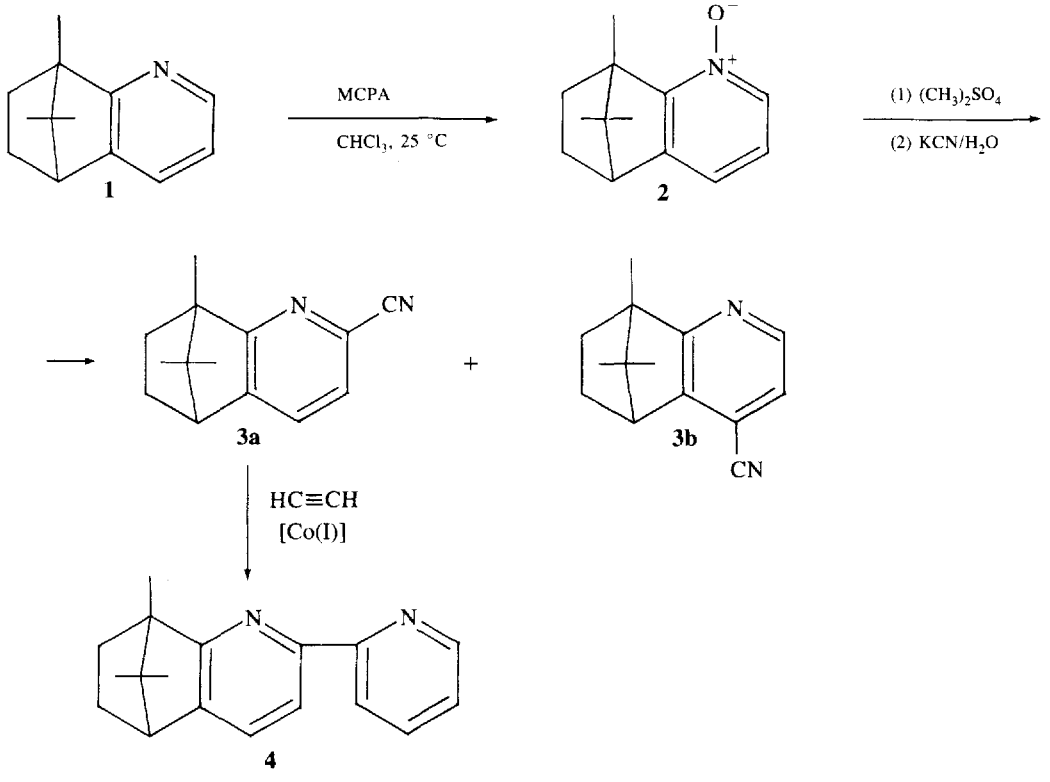
Catalytic transfer hydrogenation of acetophenone

The catalyst was prepared *in situ* by adding the required amount of the bipyridine **4** to a solution of $[Rh(COD)Cl]_2$ (2.5×10^{-5} mol) in 2-propanol (40 cm^3) under nitrogen. After addition of KOH (5×10^{-4} mol) in 5 cm^3 of 2-propanol the solution was refluxed for 1 h and then stirred overnight at room temperature before addition of the substrate acetophenone (0.01 mol). The progress of the reaction was monitored by GC (10% SP-1000 on 80/100 Supelcoport; 3 m × 3 mm, 170 C).

The product was isolated by distillation under reduced pressure after evaporation of the solvent and washing of the residue with dilute hydrochloric acid. The optical purity of the carbinol was determined in methanol solution (c = 5) using a value of $[\alpha]^{25}$ of −45.5 for the (S)-isomer.[8]

RESULTS AND DISCUSSION

The preparation of the target compound suffered from some delay due to the fact that the pyridocamphor **1**, the key intermediate of our planned synthesis, was poorly available at the beginning and our initial efforts had to be concentrated towards the set-up of an efficient procedure to add a pyridine ring onto (+)-camphor. As soon as this goal was successfully achieved and the required tetrahydroquinoline could be prepared in 52% overall yield from camphor by a three-step reaction sequence,[6] the synthesis of the bipyridine **4** was undertaken according to the synthetic route depicted in Scheme 1.



Scheme 1 [Co(I)] = (η-cyclopentadienyl)cobalt-1,5-cyclo-octadiene

Oxidation of **1** with *m*-chloroperbenzoic acid (MCPA) afforded in high yield the *N*-oxide **2** which, after alkylation with methyl sulfate, was stirred overnight with aqueous potassium cyanide. This reaction gave rise to a mixture of the isomeric nitriles **3a** and **3b** whose composition ranged, in a set of preparations, between 55:45 and 63:37, the 2-substituted product **3a** being predominant.

The different basicity of the two isomers allowed their ready separation by selective protonation with 10% hydrochloric acid and by this method the required 2-cyanotetrahydroquinoline **3a** could be recovered in pure form.

The cobalt-catalyzed co-cyclotrimerization[9] of the nitrile **3a** with acetylene completed the synthesis of the bipyridine **4**. The reaction took place smoothly in toluene at 130 °C (70% yield after 10 h), provided that a rather high amount of (η-cyclopentadienyl)cobalt-1,5-cyclo-octadiene was added as catalyst (substrate-to-metal ratio = 8−10:1). The desired bipyridine **4** was thus obtained in 20−25% overall yield from **1** and showed analytical and spectroscopic data consistent with the expected structure.

The product recovered after two separate preparations displayed $[\alpha]^{25}$ −26.6 and $[\alpha]^{25}$ −26.4 respectively, indicative that the synthetic scheme employed is racemization-free. This conclusion is supported also by the following considerations: (i) no reaction involves directly any of the asymmetric centers of the substrates; and (ii) if this should be the case, rearrangement or fragmentation of the bicyclic bornane skeleton should be expected. We believe then that the optical purity of the new ligand that has been prepared is the same as that of the tetrahydroquinoline **1** and, hence,[6] the same as that of the (+)-camphor used as the starting chiron (97%), and that the value $[\alpha]^{25}$ −27 ± 1 can be confidently assumed as the maximum optical rotatory power for **4**.

Catalytic experiments of transfer hydrogenation were run on acetophenone under experimental conditions strictly comparable with those employed in our previous work[5] and the results obtained are summarized in Table 1.

A general feature of this set of catalytic runs is that in most experiments a black precipitate separated, either during the preactivation of the catalytic solution or after the addition of the acetophenone. As this precipitate did not show any significative absorption in the IR spectrum and was quite insoluble both in water and in all the usual organic solvents, it was assumed to be rhodium metal.

The amount of the solid separated, although not exactly quantified, seemed inversely proportional to the ligand concentration. Trace amounts of metal were observed even at a ligand-to-metal ratio of 10:1 and only in the runs at 25:1 ratio was the solution maintained strictly homogeneous all the time. Although we have checked (by duplicate experiments) that this defective homogeneity does not affect the reproducibility and the reliability of the results reported in the Table, their rationalization becomes rather questionable since the actual concentration of the homogeneous catalyst in almost every run is lower than expected and substantially undetermined.

This notwithstanding, some conclusions can however be drawn: first of all that the species active in promoting the transfer hydrogenation are soluble rhodium complexes. In fact, the solid precipitated during the catalytic runs is devoid of any catalytic activity, since no reaction occurred when it was filtered and put into reaction again.

Since the concentration of the homogeneous catalyst increases on increasing the ligand-to-metal ratio, a rationale for the positive dependence of reaction rate on the concentration of the bipyridine may be inferred.

It seems reasonable that the separation of rhodium metal is determined by the presence in the catalytic solution of a rather high concentration of rhodium(I)

Table 1 Reduction of acetophenone by hydrogen transfer from 2-propanol catalyzed by $[Rh(COD)Cl]_2$ and the chiral bipyridine **4** (reaction conditions: 2.5×10^{-5} mol of $[Rh(COD)Cl]_2$ in 45 cm^3 of 2-propanol; [substrate]/[KOH]/[Rh] = 200:10:1; *T* 83 °C)

Run	[Ligand]/[Rh]	T.N.[a]	Configuration	Optical yield[b] (%)
1	0	>1[c]	—	—
2	1	6[c]	n.d.[d]	—
3	2	42	*S*	9.4
4	5	37	*R*	1.4
5	10	100	*S*	1.4
6	25	142	*R*	0.5

[a]T.N., turnover number = mols of substrate converted per hour and g-atom of rhodium. [b]Extrapolated to 100% optical purity of the ligand. [c]Percentage conversion after 12 h. [d]n.d., not determined.

species that are not coordinated to the nitrogen ligand. Actually, we have checked that, in the absence of bipyridine, the procatalyst $[Rh(COD)Cl]_2$ (COD: 1,5-cyclo-octadiene) is readily and quantitatively reduced in the early stages of the preactivation procedure.

Following these arguments, it is inferred that the coordination equilibria that involve the metal and the alkylbipyridine **4** are rather unfavourable and that a substantial excess of ligand is required in order to shift the reaction towards the formation of the catalytic species.

No conclusive evidence of the nature of the rhodium(I) adducts that are the active catalysts in the asymmetric transfer hydrogenation of acetophenone is available.

According to reports by Mestroni and co-workers[10] on rhodium(I) catalysts containing unsubstituted 2,2′-bipyridine, and taking into account our previous results on this subject,[4,5] we are inclined to believe that in our experiments the catalytically active species are more than one and that the stereoselectivity of the reaction is determined by a delicate balance between the concentration and the activity of the different rhodium complexes present in solution.

It is our belief that in this case the high amounts of ligand available in solution and the steric hindrance displayed by the alkyl substituent substantially differentiate the coordinative ability of the two nitrogen atoms within the same molecule and may favour the coordination of the bipyridine in a monodentate fashion.

This fact would give rise to species containing more than one molecule of ligand coordinated through the nitrogen of the unsubstituted heterocyclic ring, whose concentration increases on increasing the ligand-to-metal ratio. For intuitive reasons, such catalytic systems containing a 'monodentate' bipyridine are expected to be poorly efficient in the transmission of the chiral information and the erratic chirality recorded in the catalytic runs may be read as a piece of evidence supporting this speculative view.

In fact, the optical yields obtained in the asymmetric transfer hydrogenation of acetophenone with this new bipyridine are on the whole somewhat lower than those previously recorded by us with analogous ligands bearing more flexible alkyl substituents.[4] It seems then more appropriate that a certain degree of conformational freedom is maintained in the chiral target of this kind of bidentate nitrogen ligands in order to avoid substantial modifications of their coordinative behaviour.

According to this assumption, further work on this subject is in progress in our laboratories.

Acknowledgements The financial support from Ministero della Pubblica Istruzione, Rome, is gratefully acknowledged.

REFERENCES

1. Botteghi, C, Chelucci, G, Gladiali, S and Soccolini, F Italian Patent 21226 A/83, 1983
2. Botteghi, C, Caccia, G, Chelucci, G and Soccolini, F *J. Org. Chem.*, 1984, 49: 4290
3. Chelucci, G, Soccolini, F and Botteghi, C *Synthetic Commun.*, 1985, 15: 807
4. Botteghi, C, Chelucci, G, Chessa, G, Delogu, G, Gladiali, S and Soccolini, F *J. Organomet. Chem.*, 1986, 304: 217
5. Gladiali, S, Chelucci, G, Chessa, G, Delogu, G and Soccolini, F *J. Organomet. Chem.*, 1987, 3: C15
6. Chelucci, G, Delogu, G, Gladiali, S and Soccolini, F *J. Heterocycl. Chem.*, 1986, 23: 1395
7. Bonnemann, H, Brijoux, W, Brinkmann, R, Meurers, W, Mynott, R, Von Philipsborn, W and Egolf, T *J. Organomet. Chem.*, 1984, 272: 231
8. Huisgen, R and Ruchardt, C *Liebigs Ann.*, 1956, 601: 1
9. Bonnemann, H and Brijoux, W The cobalt-catalyzed synthesis of pyridine and its derivatives. In: *Aspects of Homogeneous Catalysis*, Ugo, R (ed), D. Reidel Publishing Co., Dordrecht, 1984, vol. 5, p 75
10. Mestroni, G, Spogliarich, R, Camus, A, Martinelli, F and Zassinovich, G *J. Organomet. Chem.*, 1978, 157: 345