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Approaches towards catalytic asymmetric epoxidations with methyltrioxorhenium(VII) (MTO): Synthesis and evaluation of chiral non-racemic 2-substituted pyridines

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Abstract

Efforts were made at obtaining good enantioselectivities in the epoxidation of simple olefins using methyltrioxorhenium(VII) (MTO) catalyst, urea-hydrogen peroxide (UHP) and six different chiral non-racemic 2-substituted pyridine ligands (four of which are completely novel). UHP was chosen as the hydrogen peroxide source to avoid unfavorable competition from water for vacant sites on the metal. The ligands were chosen because of putative formation of stable 5- and 6-membered chelates with the metal centre. All were synthesised in an efficient manner. Enantioselective epoxidations took place (3–12% ee) with some very good conversions.

Keywords: Methyltrioxorhenium(VII); Asymmetric catalysis; Epoxidation; Chiral pyridines

1. Introduction

In 1991, the group of Herrmann [1] made a very significant discovery when they showed that methyltrioxorhenium(VII) (MTO) acts as an efficient catalyst for olefin epoxidation in the presence of H_2O_2. Later in 1996, Sharpless and co-workers [2] demonstrated that catalytic quantities of pyridine could enhance both reaction rate and selectivity via a process of ligand acceleration on the part of this aromatic amine ligand. It was found that lower pyridine loadings (for example, 1 mol%) resulted in poor conversions and decomposition of the MTO within about 5 min and an excess of pyridine (12 mol%) relative to MTO gave optimum results [2]. Due to the high efficiency, selectivity and simplicity of this catalytic epoxidation reaction, the obtention of an asymmetric version of this reaction would indeed be a very rewarding discovery. Despite this attraction, there have been few reports on asymmetric versions of this reaction. The studies that have been reported indicate very low to moderate enantioselectivities [3–7]. For instance, Herrmann's group [3] looked at Troger's base as a possible chiral ligand for this reaction with simple olefins, and though it was possible to form a complex between this amine and MTO, the reaction was completely non-enantioselective. Rudler and co-workers [4] also failed to obtain any enantioselectivity when they used the complex formed between MTO and (−)-(4,5)-pinenebipyridine in an epoxidation reaction with 2-methyl-1-heptene. Yoon and co-workers [5,6] used a number of chiral pyridinamides, bis-amines and bis-oxazolines in the reaction with styrene, *cis*- and *trans*-methylstyrene, but only enantioselectivities of less than 10% ee were obtained. Corma and co-workers [7] have reported the epoxidation of *cis*-β-methylstyrene with (*R*)-(+)-1-phenylethylamine at −5 °C with a moderate yet significant ee of 36%, however, the conversion was very low (10%, using an excess of the olefin) and in many cases the selectivity for epoxide formation was unsatisfactory. Very recently, Herrmann and co-workers [8] achieved the highest ee (41%) thus far reported for this reaction using a chiral diol derived from (+)-tartaric acid, unfortunately the reaction was conducted at a low temperature (−30 °C) using aqueous H_2O_2, and the conversion was very poor (5%). Encouraged

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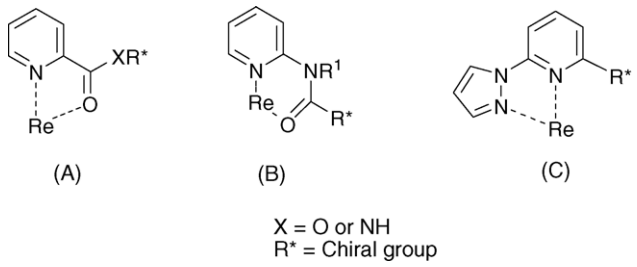


Scheme 1. 2-Substituted pyridine ligand system types and their putative mode of complexation with rhenium.

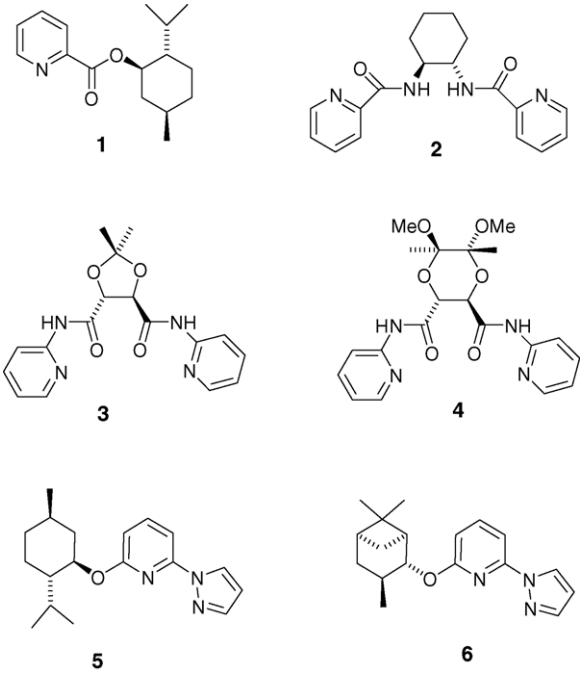
by the results of Herrmann and co-workers [8] we now wish to report our preliminary results on the catalytic asymmetric epoxidation of olefins using MTO and urea-hydrogen peroxide (UHP) with a series of chiral non-racemic 2-substituted pyridines.

We were interested in examining the behaviour of three types of 2-substituted pyridine systems for the epoxidation of olefins with MTO/UHP (types A–C, Scheme 1). These substituted pyridine systems should be ideal for such an asymmetric transformation owing to the fact that a stable 5-membered chelate complex (types A and C) and a 6-membered chelate complex (type B) could be formed [9,10]. Interestingly, a number of chiral pyridine–pyrazole complexes of type C have been employed successfully in the copper and rhodium catalysed cyclopropanation of styrene [11]. Of note is the oxobisperoxy molybdenum complex derived from an analogous pyridine–pyrazole ligand and used successfully by Thiel [12] for catalytic asymmetric epoxidations. Besides these precedents from the literature for putative bi-dentate complex formation between rhenium and various 2-substituted ligands, this mode of chelation with the Re metal centre of MTO was expected on the basis that Kühn and co-workers [13] and Rudler and co-workers [4] showed that 1,10-phenanthroline, 4,7-dimethyl-1,10-phenanthroline, (−)-(4,5)-pinenebipyridine and other bi-dentate pyridines form stable bidentate complexes with MTO.

2. Results and discussion

With this strategy in mind, the following 2-substituted pyridines (Scheme 2) were prepared for use in the MTO/UHP epoxidation of olefins.

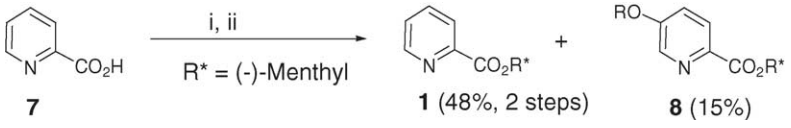
Within this group of ligands it was expected that ligand **1**, **5** and **6** would form a mononuclear complex with MTO, whilst the C_2-symmetric ligands (**2**–**4**) would form bi-nuclear complexes with MTO.



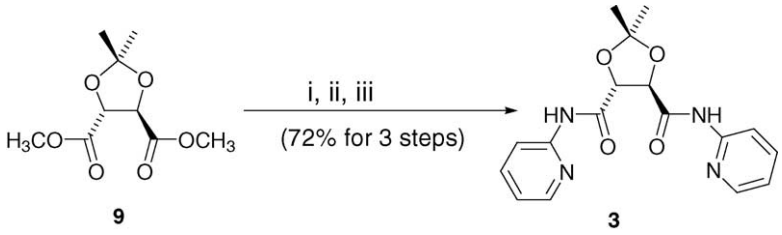
Scheme 2. Chiral pyridine-ester and pyridine-amide ligands prepared for use in the MTO/UHP epoxidation of olefins.

(−)-Menthyl 2-pyridinecarboxylate (picolinate) **1** was the first 2-substituted pyridine ligand to be prepared via treatment of picolinic acid chloride with menthol alkoxide (Scheme 3). Besides furnishing the desired ester **1** in satisfactory yield from picolinic acid, 5-menthoxy (−)-menthyl 2-pyridinecarboxylate **8** was obtained in low yield. This is not surprising owing to the electrophilic nature of the 5-position in 2-pyridinecarboxylates. In fact during the course of our studies on the synthesis of chiral 2-(2-pyridinyl)oxazolines [14] we observed formation of undesirable 2-[2-(4-methoxyl)pyridinyl]oxazoline adducts on using hydroxide/methanol to convert the corresponding chloropyridinecarboxamide precursor to the desired product.

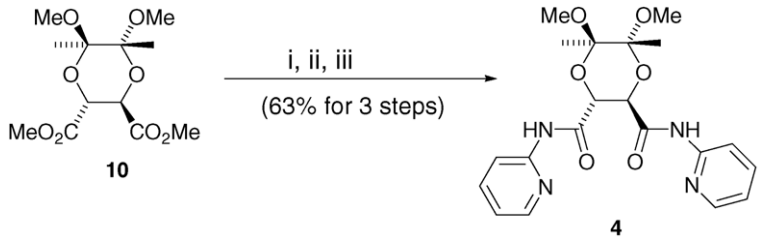
(1*R*,2*R*)-*N*,*N*′-2-bis(2-pyridinecarboxamide)-1, 2-cyclohexane **2** – a well known ligand which has been used previously for molybdenum catalysed asymmetric allylic alkylation reactions [15] – was prepared in an enantiomerically pure form {$[\alpha]_D^{24}$ −114.7 (c = 1.25 $CHCl_3$) lit. [16] $[\alpha]_D^{20}$ −106.1 (12.5 mg/mL, $CHCl_3$)} from commercial (1*R*,2*R*)-(−)-1,2-diaminocyclohexane. The isopropylidene tartrate derived bis-pyridinamide **3** was prepared from (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester **9** [17] via 2,3-*O*-isopropylidene-L-tartaric acid dichloride [18] according to the procedure given in



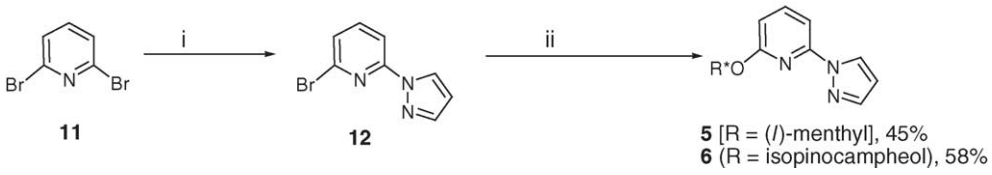
Scheme 3. (i) $SOCl_2$, reflux 13 h. (ii) (−)-Menthol, NEt_3, CH_2Cl_2, 0 °C to r.t.



Scheme 4. (i) NaOH, EtOH, r.t. 18 h, (ii) $(COCl)_2$, C_6H_6, 60–65 °C, 11 h, (iii) 2-aminopyridine, NEt_3, C_6H_6, r.t., 9 h.



Scheme 5. (i) NaOH, EtOH, 40 °C, 1.5 h then r.t. overnight, ref. [18] (ii) $(COCl)_2$, C_6H_6, 60–65 °C, 10 h, (iii) 2-aminopyridine, NEt_3, C_6H_6, r.t., 24 h.

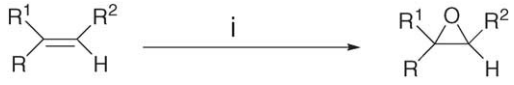


Scheme 6. (i) Potassium pyrazolate, THF, 40 °C, 1.5 h then r.t. overnight, ref. [24] (ii) NaH, DMF, (−)-menthol, 60–70 °C.

Scheme 4. The bisacetal pyridinamide **4** was obtained after much initial experimentation [19] from dimethyl (2*R*,3*R*,5*R*,6*R*)-dimethoxy-2,3-dimethyl-1,4-dioxane-5,6-dicarboxylate **10** [20] according to the procedure shown in Scheme 5. It can be seen that ligand **3** bears a resemblance to the DIOP ligand of Dang and Kagan [21] by virtue of the presence of an acetonide back-bone. The bisacetal backbone present in ligand **4** is also present in some interesting chiral bis-diphenylphosphine [22], phosphinite ligands [23] and monooxazoline carbinols [24] which have been employed in enantioselective hydrogenations, hydrosilylations and diethylzinc additions to benzaldehyde.

The ligands **5** and **6** were synthesised by treating 2-bromo-6-(1-pyrazolyl)pyridine **12** (obtained from 2,6-dibromopyridine **11** using the procedure of Jameson and Goldsby [25]) with sodium (*l*)-mentholate and sodium isopinocampheolate (Scheme 6).

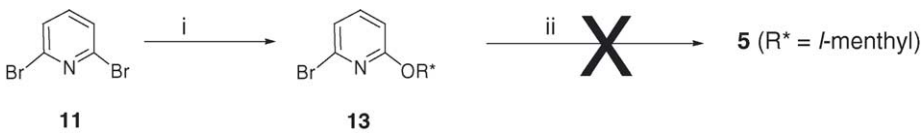
Prior to accessing ligand **5**, via the route shown in Scheme 6, we prepared 2-bromo-6-*O*-mentholatepyridine **13** according to the method of Brunner and co-workers [26] but this intermediate failed to react with potassium pyrazolate



Scheme 8. (i) MTO (0.5 mol%), UHP (1.5–2 equivalents), chiral ligand (1–12 mol%), CH_2Cl_2, r.t.

to give the pyrazole–pyridine compound **5** (Scheme 7). This was probably due to steric hindrance from the terpene side unit.

These six chiral ligands (**1**–**6**) were subsequently employed in a number of MTO catalysed epoxidation reactions with simple olefins, using UHP as an anhydrous source of H_2O_2 (Scheme 8). We choose this non-aqueous system to avoid unwanted complexation of water to the MTO and/or peroxo complexes as it was already noted that water induced ligand removal can be a problem [8], besides it has also been observed that *N*-base adducts of MTO are sensitive to water [27]. We have previously investigated this system using pyridine, pyrazole and imidazole as the amine additive [28].



Scheme 7. (i) Ref. [26] (ii) Potassium pyrazolate, THF, reflux 12 h.

Table 1
MTO catalysed epoxidation of simple olefins with chiral ligands **1**–**6**

Entry	Olefin (mmol)	Ligand (mol%)	Conditions	Reaction time (h)	Conversion[a] (%)	ee (%)
1	Styrene[b]	**2** (6)	0 °C	16	13	6
2	Styrene[c] (1)	**3** (1)	r.t.	24	36	12
3	Styrene[c] (2.6)	**3** (6)	r.t.	16	54[d]	2
4	Styrene[c] (1.8)	**3** (6)	0 °C	24	20[d]	2
5	Styrene[c] (1)	**4** (1)	r.t.	24	62	6
6	Styrene[c] (2.5)	**5** (12)	r.t.	16	7	2
7	Styrene[c] (2.5)	**6** (12)	r.t.	16	2	2
8	1-Methylcyclohexene[c] (1)	**1** (12)	r.t.	5	63[d]	9
9	1-Methylcyclohexene[c]	**2** (6)	r.t.	5	69	7
10	1-Methylcyclohexene[c] (2.5)	**3** (6)	r.t.	5	75[d]	11
11	1-Methylcyclohexene[c] (2.5)	**3** (6)	0 °C	24	90[d]	7
12	1-Methylcyclohexene[c] (1)	**4** (1)	r.t.	24	61	8
13	α-Methylstyrene[b]	**2** (6)	r.t.	3	22	7
14	α-Methylstyrene[b]	**2** (6)	0 °C	6	27	6
15	α-Methylstyrene[c] (2.7)	**3** (6)	r.t.	6	21[d]	9
16	4-Methylstyrene[c] (2.7)	**3** (6)	r.t.	16	36[d]	7
17	4-Methylstyrene[c] (2.7)	**4** (12)	r.t.	6	30[d]	7
18	4-Methylstyrene[c] (2.5)	**5** (12)	r.t.	13	17	9
19	4-Methylstyrene[c] (2.5)	**6** (12)	r.t.	13	7	12

[a] Conversion refers to the transformation of olefin to epoxide.
[b] Reaction conducted according to procedure 1 (see Section 4).
[c] Reaction conducted according to procedure 2 (see Section 4).
[d] Two equivalents of UHP were employed.

The results for these epoxidation reactions are shown in Table 1.

Firstly, it is noteworthy mentioning that the selectivity for epoxide formation was extremely good, being ≥98% in almost all cases except for entries 2, 18 and 19 where the selectivity was 92%, 90% and 86%. The principle side products in these cases were benzaldehyde and 4-methylbenzaldehyde.

It can be seen from the table that low enantioselectivities were obtained in these reactions (ee = 2–12%).

We tried to determine if there was a temperature dependence on the enantioselectivity of this reaction, as can be seen from the reaction using styrene with ligand **3** (entries 3 and 4), 1-methylcyclohexene with ligand **3** (entries 10 and 11) and α-methylstyrene with ligand **2** (entries 13 and 14). Only in the case of the epoxidation of 1-methylcyclohexene with ligand **3** was a very slight temperature dependence observed, as the ee decreased slightly as the temperature was lowered to 0 °C. In the other two cases, no temperature dependence was found.

Of the ligands tested in these reactions, the pyridine–pyrazoles **5** and **6** were the worst, in terms of both efficiency and stereoselectivity. Interestingly, Herrmann and co-workers [8] have reported using some chiral pyrazole ligands and achieved low ees in the range 6–15%.

We tried to improve the enantioselectivity by reducing the concentration of H_2O_2 in solution in order to favor the mono-peroxorhenium complex, which one would expect to complex more efficiently with a bidentate ligand than the diperoxo complex [29]. In this reaction, styrene was chosen as the substrate, 6 mol% of ligand **4** was employed along with 0.25 equivalents of UHP. However, a 19% conversion of olefin to product after 22 h at room temperature was obtained along with an ee of only 4%.

We believe that the poor enantioselectivities observed may be due to the poor coordination of our chiral ligands to the rhenium centre of MTO with continued weak coordination of these ligands to the peroxy complexes leading to low enantiofacial selectivity at the olefin double bond. It has been reported recently that there is a rapid equilibrium between the coordinated and the non-coordinated species in solution [30] and that a significant excess of the amine must be used. This hypothesis was supported by carrying out a number of ^{1}H NMR experiments where a solution of the ligand and MTO was prepared and the change in the chemical shift of the methyl group of MTO observed. All our ligands (compounds **1**–**6)** were examined in this study (Table 2). As can be seen from Table 2, the chemical shift differences were very slight ($\Delta\delta = \pm 0.04$ ppm) and this would indicate weak coordination to the metal centre of MTO [29,30]. In all cases

Table 2
Determination of the coordination strength of ligands **1**–**6** with MTO using NMR spectroscopy[a]

Ligand	Ligand:MTO	$\Delta\delta$ (ppm)
1	2:1	0
2	2:1	+0.01
3	2:1	+0.025
4	1:1	+0.04
5	2:1	0
5	10:1	+0.02
6	1:1	−0.01

[a] Measured in $CDCl_3$ at 300 K.

but one, an upfield chemical shift was observed which would indicate weak coordination of the ligand to the metal centre.

The conversions observed for these reactions were poor to very good. It was observed that no reaction took place when 1-phenylcyclohexene was used as substrate with ligands **5** and **6**. It is noteworthy to observe that in the case of the epoxidation of styrene using ligands **3** and **4**, the conversions were as good as or even better than those obtained using MTO/UHP and pyridine (12 mol%) [28], this is presumably due to some form of enhanced activating effect on the formation of the peroxo complexes by compounds **3** and **4** or enhanced activation of the peroxo complexes for oxygen transfer to the olefin.

3. Conclusions

A range of chiral bidentate pyridine ligands (**1**–**6**) was prepared from readily available starting materials, of which ligands **3**–**6** were completely novel compounds. Catalytic quantities of these ligands were then screened in the MTO catalysed epoxidation of a range of olefins using UHP at room temperature or 0 °C. Enantioselective epoxidations indeed were observed, yet despite the low ees obtained (2–12%) significant progress has been obtained which may direct further studies that can lead to successful catalytic enantioselective epoxidations of olefins with MTO/UHP.

4. Experimental

4.1. General information

(4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester **9**, dimethyl (2*R*,3*R*,5*R*,6*R*)-dimethoxy-2,3-dimethyl-1,4-dioxane-5,6-dicarboxylate **10** and (+)-isopinocampheol were prepared according to previously described procedures [17,20,32]. All other reagents were obtained from Aldrich, Lancaster or Acros.

Normal column chromatography was carried out on silica gel (sds, 70–200 μm) and flash column chromatography (Merck, 40–63 μm and sds, 40–63 μm). TLC was carried out on aluminium backed Kisel-gel 60 F_{254} plates (Merck). Plates were visualised either by UV light or phosphomolybdic acid in ethanol.

Gas chromatographic (GC) analyses of the products obtained from the epoxidation reactions were performed on a Hewlett Packard (HP) 6890 series instrument equipped with a flame ionization detector (FID). The chromatograph was fitted with a cyclodex-B capillary column (30 m, 250 μm, 0.25 μm) (Agilent 112–2532).

In all cases, the olefin conversions were calculated by simply determining the ratio of the peak areas for the olefin substrate and the epoxide product.

Melting points were recorded on a leica Galen III apparatus and they are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Bruker AMX300 (^{1}H: 300.13 MHz and ^{13}C: 75 MHz) or a Bruker Avance (^{1}H: 400.13 MHz and ^{13}C: 100.61 MHz) instrument using $CDCl_3$ as solvent and TMS as internal standard (for measurements made with the Bruker AMX300 instrument) and the signal from residual $CHCl_3$ as an internal standard (for the measurements made with the Bruker Avance instrument). ^{13}C NMR spectra were obtained with 135° DEPT editing to identify methylene groups. Mass spectra were recorded on a VG Autospec M spectrometer using the FAB technique. Infra-red spectra were measured with a Perkin-Elmer Paragon 1000 model. Optical rotations were measured with a Perkin-Elmer 241 polarimeter using a 10 cm cell and the concentrations are quoted in g/100 mL. Elemental analyses were performed by the microanalysis service at the CACTI centre in the University of Vigo, Spain.

4.2. Catalytic reactions

General procedures for the MTO–UHP catalysed epoxidation of olefins with chiral ligands **1**–**6**.

4.2.1. Procedure 1 (Table 2)

Methyltrioxorhenium(VII) (0.5 mol%) and the chiral ligand were dissolved in anhydrous dichloromethane and stirred at room temperature for 10 min. UHP (Aldrich) was then added and the mixture stirred for a further 15 min. The olefin was added neat or as a solution in anhydrous dichloromethane and the reaction mixture was stirred at room temperature for a period of time. A catalytic quantity of manganese dioxide and crushed ice were then added and the mixture stirred for a further 1 h. The organic phase was separated, and the aqueous phase extracted with dichloromethane. The combined organic phases were dried with anhydrous sodium sulphate. After filtration, an aliquot of filtrate was removed for GC analysis.

4.2.2. Procedure 2

Methyltrioxorhenium(VII) (6.2 mg, 0.025 mmol), UHP (0.706 g, 6.75 mmol) and the chiral ligand (6 or 12 mol%) were dissolved in anhydrous dichloromethane (4 mL) and stirred at room temperature. The olefin (5 mmol) was subsequently added and the reaction mixture stirred for 3–24 h. Dichloromethane (10 mL) was then added and the organic phase washed with water (4× 10 mL) followed by saturated aqueous sodium thiosulphate water (4× 10 mL). The organic phase was separated and dried with anhydrous magnesium sulphate. After filtration the solvent was removed under vacuum and a sample of the crude product analysed by GC.

4.3. Preparation of ligands

4.3.1. Synthesis of 2-[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl]pyridine carboxylate 1

Thionyl chloride (17 mL, 87.6 mmol) was added to picolinic acid (3 g, 24.4 mmol) at room temperature and the

mixture was heated to reflux and maintained at reflux for 14 h. The solvents were then evaporated in vacuo and the residual thionyl chloride removed by adding more benzene (2× 5 mL). The acid chloride which resulted was dissolved in dry dichloromethane (5 mL) and this solution was added slowly to a mixture of (−)-menthol (4 g, 26 mmol) and dry triethylamine (7 mL, 51 mmol) in dry dichloromethane (5 mL) at 0 °C under an atmosphere of nitrogen. The reaction mixture was warmed to room temperature and stirred at this temperature overnight. Brine (20 mL) was added and the reaction mixture extracted with dichloromethane (3× 20 mL). The combined organic phases were dried, filtered and evaporated in vacuo to give a dark semi-solid (6.87 g). This was purified by silica gel flash chromatography (v/v, 10:1—hexane:EtOAc) which afforded two bands.

4.3.1.1. Band 1. Title compound: colourless oil (3.06 g, 48%); $[\alpha]_D^{18}$ −69.6 (c = 0.47, $CHCl_3$), $[\alpha]_D^{23}$ −86.6 (c = 4.7, MeOH), lit. [33] $[\alpha]_D^{20}$ −102.5 (c = 5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) 8.79 (d, J = 4 Hz, 1H, H-6), 8.12 (d, J = 4 Hz, 1H, H-3), 7.85 (td, J = 7.7, 1.7 Hz, 1H, H-4), 7.47 (qd, J = 7.6, 4.8, 1 Hz, 1H, H-5), 5.05 (td, J = 10.9, 4.4 Hz, 1H, *H*CO), 2.15–2.01 (m, 1H), 2–1.93 (m, 1H), 1.76–1.53 (m, 4H), 1.26–1.07 (m, 3H), 0.92 (d, J = 6.7 Hz, 3H, (C*H*$_3$)CHCH$_3$), 0.90 (d, J = 7.2 Hz, 3H, (CH$_3$)CHC*H*$_3$), 0.79 (d, J = 7 Hz, 3H, (C*H*$_3$)CHCH$_2$).

4.3.1.2. Band 2. 5-Menthoxy(−)-menthyl 2-pyridinecarboxylate **8**, colourless oil (1.51 g, 15%), $[\alpha]_D^{21}$ −61.1 (c = 1.08, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 8.67 (d, J = 4.8 Hz, 1H, H-3), 8.10 (d, J = 4 Hz, 1H, H-6), 7.47 (dd, J = 5.3, 2.1 Hz, 1H, H-4), 5.06 (td, J = 11, 4.5 Hz, 1H, *H*COCO), 3.41 (m, 1H, *H*CO), 2.15–2.14 (m, 1H), 1.99–1.94 (m, 1H), 1.77–1.76 (m, 1H), 1.72–1.69 (m, 1H), 1.65–1.59 (m, 2H), 0.95–0.91 (m, 12 H), 0.83–0.79 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 163.55, 150.78, 150.63, 149.84, 145.33, 126.80, 125.55, 76.44, 71.51, 50.13, 46.86, 45.05 (CH_2), 40.67 (CH_2), 34.53 (CH_2), 34.16 (CH_2), 31.61, 31.49, 26.31, 25.84, 23.41 (CH_2), 23.15 (CH_2), 22.17, 21.96, 20.96, 20.70, 16.25, 16.09; FAB-MS (*m*/*z*): 416 (*M* + 1, 5%).

4.3.2. N,N′-Bis(2-pyridyl)-(4R,5R)-2,2-dimethyl-[1,3]-dioxolane-4,5-dicarboxamide 3

Dimethyl 2,3-isopropylidene-L-tartrate **9** (2.5 g, 11.5 mmol) in ethanol (3.0 mL) was added to a sodium hydroxide (0.93 g, 23 mmol) solution in ethanol (10 mL). After the mixture was stirred at room temperature for 18 h, ethanol was removed under reduced pressure to give 2,3-*O*-isopropylidene-L-tartrate acid disodium salt (2.7 g) as a white powder. Oxalyl chloride (0.4 g, 3.1 mmol) in anhydrous benzene (2 mL) was added to 2,3-*O*-isopropylidene-L-tartrate acid disodium salt (0.24 g, 1.0 mmol) suspended in anhydrous benzene (5 mL), and the mixture was stirred at 60–65 °C for 11.5 h. The solvent and excess oxalyl chloride was removed under reduced pressure. Anhydrous benzene (4 mL ×2) was added and evaporated under reduced pressure, in order to completely remove the oxalyl chloride. A solution of 2-aminopyridine (0.3 g, 3.2 mmol) and triethylamine (0.3 g, 3 mmol) in benzene (3 mL) was added to the residue suspended in anhydrous benzene (5 mL) at room temperature. After the mixture was stirred at room temperature for 9 h, water (3 mL) and benzene (8 mL) were added to dissolve the residue. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (4 mL ×3). The combined organic layers were dried over anhydrous magnesium sulphate. After filtration, the filtrate was concentrated under reduced pressure to afford an oily residue, which was purified by flash column chromatography with hexane-ethyl acetate (v/v, 4:1 and 2:1 successively) to give the *title compound* which was recrystallized from hexane-ethyl acetate to give a white crystalline solid (0.25 g, 72%). m.p. 172.3–173.9 °C; $[\alpha]_D^{18}$ −208.1 (c = 0.7, $CHCl_3$); IR (KBr) ν_{max} 3251 (NH), 1687 (C=O), 1580, 1435, 1305, 1091, 780 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 9.18 (s (br), 2H, CON*H*), 8.34 (m, 2H, H-6), 8.29 (d, J = 8.1 Hz, 2H, H-3), 7.74 (td, J = 8.1, 1.8 Hz, 2H, H-4), 7.09 (dd, J = 8.1, 5.1 Hz, 2H, H-5), 4.91 (s, 2H, C*H*O), 1.60 (s, 6H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 168.24, 150.41, 148.10, 138.53, 120.45, 114.19, 113.54, 77.69, 26.18; FAB-MS (m/z): 345 (*M* + 3, 3), 344 (*M* + 2, 21), 343 (*M* + 1, 100%); $C_{17}H_{18}N_4O_4$ requires: C, 59.64; H, 5.30; N, 16.36% found: C, 59.69; H, 5.44; N, 16.47%.

4.3.3. N,N′-Bis(2-pyridyl)-(2R,3R,5R,6R)-2,3-dimethoxy-2,3-dimethyl-[1,4]-dioxane-5,6-dicarboxamide 4

Oxalyl chloride (0.60 g, 4.7 mmol) in anhydrous benzene (3 mL) was added to (2*R*,3*R*,5*R*,6*R*)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane-5,6-dicarboxilic acid disodium salt (0.45 g, 1.5 mmol) suspended in anhydrous benzene (4 mL). The mixture was stirred at room temperature for 1 h, and at 60–65 °C for 10h. The solvent was removed in vacuo and the unreacted oxalyl chloride was removed by treating the residue with anhydrous benzene (4 mL ×2). 2-Aminopyridine (0.31 g, 3.3 mmol) and triethylamine (0.62 g, 6.2 mmol) in benzene (5 mL) were added to the residue suspended in anhydrous benzene (4 mL) and the reaction mixture stirred at room temperature for 24 h. Water (3 mL) and benzene (8 mL) were added to quench the reaction and dissolve the residue. The organic layers were separated, and the aqueous layer was extracted with dichloromethane (4 mL ×3). The combined organic layers were dried over anhydrous magnesium sulphate. After filtration, the filtrate was concentrated under reduced pressure to give an oily residue, which was purified by silica gel flash column chromatography with hexane-ethyl acetate (v/v, 2.5:1, 2:1 and 1.5:1 successively) affording a brownish yellow gum which was crystallized from hexane-ethyl acetate to give a white powder (0.39 g, 63%). m.p. 81.7–82.4 °C; $[\alpha]_D^{18}$ −88.7 (c = 2.7, $CHCl_3$); IR (KBr): 3396 (NH), 1700 (C=O), 1587, 1519,

1435, 1303, 1145, 1114, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ppm) 8.87 (s(br), 2H, CON*H*), 8.30-8.25 (m, 4H, H-6, H-3), 7.68 (td, $J = 7.5$, 2.1 Hz, 2H, H-4), 7.06–7.02 (m, 2H, H-5), 4.57 (s, 2H, C*H*O), 3.24 (s, 6H, OCH_3), 1.39 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 166.21, 150.78, 147.81, 138.45, 120.12, 114.41, 99.82, 71.08, 48.57, 17.70; FAB-MS (*m*/*z*): 417 ($M + 1$, 100), 418 ($M + 2$, 24%); $C_{20}H_{24}N_4O_6$ requires: C, 57.69; H, 5.81; N, 13.45 found: C, 57.41; H, 5.95; N, 13.30%.

4.3.4. 2-(1-Pyrazolyl)-6-[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl-oxy]-pyridine 5

To 60% sodium hydride (0.64 g, 26 mmol) suspended in DMF (2 mL), was added (−)-menthol (1.4 g, 8.9 mmol) in DMF (10 mL). After the mixture was stirred for 15 min at 60–70 °C, 2-bromo-6-(1-pyrazolyl) pyridine **12** [25] (2 g, 8.9 mmol) in DMF (5 mL) was added. The mixture was stirred at 60–70 °C for another 10 h overnight. After the DMF was removed under reduced pressure, the residue was partitioned between dichloromethane (20 mL) and saturated aqueous sodium chloride (20 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (20 mL ×2). The organic layers were combined, washed with saturated aqueous sodium chloride (20 mL ×2), and dried over anhydrous magnesium sulphate. After filtration, the filtrate was concentrated under reduced pressure to give the crude product (2.8 g), which was purified by column chromatography with hexane-ethyl acetate (v/v, 25:1) furnishing the *title compound* as a colourless solid (1.19 g, 45%). m.p. 75–77 °C; $[\alpha]_D^{18}$ −193.6 ($c = 0.3$, $CHCl_3$); IR (KBr), ν_{max} 2957, 2871, 2927, 2845, 1609, 1575, 1519, 1462, 799, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 8.45–8.44 (m, 1H), 7.72–7.71 (m, 1H), 7.66 (t, $J = 8.1$, 1H), 7.47 (dd, $J = 7.8$, 0.6, 1H), 6.57 (dd, $J = 8.1$, 0.6, 1H), 6.44 (dd, $J = 2.4$, 1.8, 1H), 5.02 (td, $J = 10.8$, 1.2, 1H), 2.26–2.2 (m, 1H), 2.1–2.04 (m 1H), 1.77–1.71 (m, 2H), 1.59–1.51 (m, 2H), 1.26–1.01 (m, 3H), 0.93 (t, $J = 7.2$, 6H), 0.78 (d, $J = 6.9$, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm), 162.75, 149.35, 141.78, 140.99, 126.83, 108.39, 107.28, 103.35, 75.32, 47.61, 40.3, 34.52, 31,64, 26.29, 23.77, 22.23, 20.73, 16.65; FAB-MS (*m*/*z*) 300 ($M + 1$, 37), 299 (M, 11) and 162 ($M + 1$-$C_{10}H_{18}$, 100%);. $C_{18}H_{25}N_3O$ requires: C, 72.21; H, 8.42; N, 14.03% found: C, 72.21; H, 8.42; N, 14.04%.

4.3.5. 2-(1-Pyrazolyl)-6-[-1R(1α,2β,3α,5α)-(2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yloxy)-pyridine 6

The *title compound* was prepared according to the procedure for compound **5** where the 2-bromo-6-(1-pyrazolyl) pyridine **12** [25] (1.39 g, 6.2 mmol) was coupled with (+)-isopinocampheol [31] (0.96 g, 6.2 mmol) to give the *title compound* (1.07 g, 58%) as a colourless solid after purification by column chromatography (hexane:EtOAc—25:1).

m.p. 71–74 °C; $[\alpha]_D^{18}$ −96.4 ($c = 0.4$, $CHCl_3$); IR (KBr), ν_{max} 2906, 1604, 1573, 1518, 1464, 1345, 1139, 1039, 990, 799, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 8.48 (d, $J = 2.7$, 1H), 7.72 (d, $J = 1$, 1H), 7.70 (t, $J = 7.8$, 1H), 7.48 (d, $J = 7.8$ Hz, 1H), 6.61 (d, $J = 8.1$ Hz, 1H), 6.45–6.44 (m, 1H), 5.33 (m, 1H, CHO), 2.80–2.78 (m, 1H), 2.43–2.31 (m, 2H), 2–1.97 (m, 1H), 1.92–1.88 (m, 1H), 1.84–1.77 (m, 1H), 1.28 (s, 3H), 1.26 (m, 1H), 1.18 (d, $J = 7.2$, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm), 162.77, 149.37, 141.79, 140.79, 126.80, 108.64, 107.31, 103.32, 75.61, 47.73, 43.91, 41.52, 38.43, 36.3 (CH_2), 33.57 (CH_2), 27.57, 23,87, 20.92; FAB-MS (*m*/*z*): 299 ($M + 2$, 5), 298 ($M + 1$, 20), 297 (M, 5) and 162 ($M + 1$-$C_{10}H_{18}$, 100%);. $C_{18}H_{25}N_3O$ HRMS (FAB) found, 347.1747; $C_{18}H_{25}N_3O$ requires 347.1760.

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References

[1] (a) W.A. Herrmann, R.W. Fischer, D.W. Marz, Angew. Chem. Int. Ed. Engl. 30 (1991) 1638;
(b) F.E. Kühn, A. Scherbaum, W.A. Herrmann, J. Organomet. Chem. 689 (2004) 4149.
[2] J. Rudolph, K.L. Reddy, J.P. Chiang, K.B. Sharpless, J. Am. Chem. Soc. 119 (1997) 6189.
[3] W.A. Herrmann, F.E. Kühn, M.R. Mattner, G.R.J. Artus, M.R. Geisberger, J.D.G. Correia, J. Organomet. Chem. 538 (1997) 203.
[4] H. Rudler, J.R. Gregorio, B. Denise, J.-M. Brégeault, A. Deloffre, J. Mol. Catal. A Chem. 133 (1998) 255.
[5] S.-W. Park, K.-J. Kim, S.S. Yoon, Bull. Korean Chem. Soc. 21 (2000) 446.
[6] S.-W. Park, S.S. Yoon, J. Korean Chem. Soc. 44 (2000) 81.
[7] M.J. Sabater, M.E. Domine, A. Corma, J. Catal. 210 (2002) 192.
[8] J.J. Haider, R.M. Kratzer, W.A. Herrmann, J. Zhao, F.E. Kühn, J. Organomet. Chem. 689 (2004) 3735.
[9] C. Moberg, H. Adolfsson, K. Warnmark, Acta Chem. Scand. 50 (1996) 195 (and references cited therein).
[10] A.L. Gavrilova, B. Bosnich, Chem. Rev. 104 (2004) 349 (and references cited therein).
[11] D.L. Christenson, C.J. Tokar, W.B. Tolman, Organometallics 14 (1995) 2148.
[12] W.R. Thiel, J. Mol. Catal. A Chem. 117 (1997) 449 (and references cited therein).
[13] P. Ferreira, W.-M. Xue, É. Bencze, E. Herdtweck, F.E. Kühn, Inorg. Chem. 40 (2001) 5834.
[14] Y.-E. Guo, A.J. Burke, Unpublished results.

[15] B.M. Trost, I.J. Hachiya, Am. Chem. Soc. 120 (1998) 1104.
[16] C. Moberg, Department of Organic Chemistry, KTH Chemistry, Stockholm, Sweden, Personal communication.
[17] E.A. Mash, K.A. Nelson, S. van Deusen, S.B. Hemperly, Org. Synth. 68 (1990) 92–103.
[18] N. Arnaud, C. Picard, L. Cazaux, P. Tisnès, Tetrahedron 53 (1997) 13757.
[19] A.J. Burke, A.I. Pisco, E.P. Carreiro, Unpublished results.
[20] M.T. Barros, A.J. Burke, C.D. Maycock, Tetrahedron Lett. 40 (1999) 1583.
[21] T. Dang, H.B. Kagan, J. Am. Chem. Soc. 94 (1972) 6430.
[22] U. Berens, R. Selke, Tetrahedron Asymmetry 7 (1996) 2055.
[23] D. Haag, J. Runsink, H.-D. Scharf, Organometallics 17 (1998) 398.
[24] M.T. Barros, C.D. Maycock, A.M.F. Phillips, Eur. J. Org. Chem. (2004) 1820.
[25] D.L. Jameson, K.A. Goldsby, J. Org. Chem. 55 (1990) 4992.
[26] H. Brunner, R.J. Maier, M. Zabel, Synthesis (2001) 2484.
[27] F.E. Kühn, A.M. Santos, P.W. Roesky, E. Herdtweck, W. Scherer, P. Gisdakis, I.V. Yudanov, C. Di Valentin, N. Rosch, Chem. Eur. J. 12 (1999) 3603.
[28] E.P. Carreiro, A.J. Burke, M.J.M. Curto, A.J.R. Teixeira, J. Mol. Catal. A Chem. 217 (2004) 69.
[29] H. Adolfsson, C. Copéret, J.P. Chiang, A.K. Yudin, J. Org. Chem. 65 (2000) 8651 (and references cited therein).
[30] F.E. Kühn, A.M. Santos, I.S. Gonçalves, C.C. Romão, A.D. Lopes, Appl. Organomet. Chem. 15 (2001) 43.
[31] W.A. Herrmann, F.E. Kühn, M.U. Rauch, J.D.G. Correia, G. Artus, Inorg. Chem. 34 (1995) 2914.
[32] C.F. Lane, J.J. Daniels, Org. Synth. Col. 6 (1988) 719.
[33] O. Cervinka, O. Kriz, Z. Chem. 12 (1972) 135 (This paper gave only a specific rotation and boiling point for compound 1).