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Enantiomerically pure α-pinene derivatives from material of 65% enantiomeric purity. Part 1: Di[3α-(2α-hydroxy)pinane]amine†

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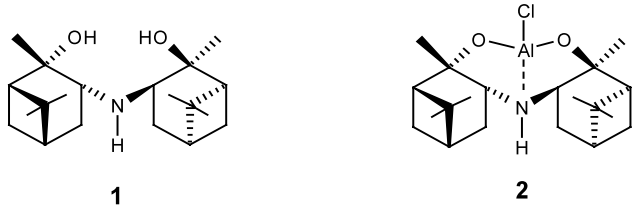
Abstract—By making use of differences in the physical properties of crystallographically different heteroenantiomeric racemic compounds and pure enantiomers, a convenient method for the preparation of enantiomerically pure 2α-hydroxypinan-3-one and its oxime was developed. The enantiomerically pure compounds were used in syntheses of pinane amino alcohols, which proved to be useful ligands for catalytic applications in processes such as asymmetric reduction of prochiral ketones, asymmetric alkylation of aldehydes, and Diels–Alder reactions. Optically active *tert*-butylphenylphosphinothioic acid was found to be a versatile chiral solvating agent for the rapid determination of enantiomeric excess of the above compounds by ^{1}H NMR spectroscopy.

1. Introduction

Since the pioneering work of Brown,[1] pinene and its numerous derivatives, such as pinanediol, 2α-hydroxypinan-3-one, Alpine-Borane, and *B*-chlorodiisopinocampheylborane, have been widely applied in asymmetric synthesis with great success.[2] The ready availability of both enantiomers of α-pinene makes this compound unique among natural sources of chirality. 2α-Hydroxypinan-3-one, synthesised by treatment of α-pinene with potassium permanganate in aqueous acetone solution,[3] has been successfully used as a chiral auxiliary in the asymmetric alkylation of its ketoimines for over 20 years. The use of 2-α-hydroxypinan-3-one in numerous syntheses, especially of amino acids, α,α-disubstituted amino acids and sphingosines[4] has resulted in the commercial availability of this compound. However, the mixture of enantiomers of about 91% enantiomeric purity[5] is the most commonly available.

Optically active 2α-hydroxypinane-3-one is a source of optically active amino alcohols via its oxime[6] or the Schiff bases formed with alkyl(aryl)amines.[7] Borolidines of these amino alcohols have been applied as catalysts in the asymmetric reduction of prochiral ketones.[8] Amino alcohols can also be employed as potential chiral ligands for other processes. We therefore turned our attention toward di[3α-(2α-hydroxy)-pinane]amine **1** (Fig. 1) (a precursor of C_2-symmetric catalysts of the type **2**), which is expected to be easily obtained and should be useful as a catalytic ligand for asymmetric Diels–Alder reactions.



1 **2**

Figure 1.

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Since it is impossible to foresee the direction of non-linear induction effects, it was necessary to employ enantiomerically pure compounds. Therefore, we directed our attention towards the development of convenient methods for the production of enantiomerically pure (−)-2α-hydroxypinan-3-one and its oxime from the readily available and inexpensive (+)-α-pinene of low enantiomeric purity (ca. 65%).

2. Results and discussion

It was observed earlier[7] that Schiff bases from the reaction of partially enantiomerically enriched 2α-hydroxypinan-3-one, (65% e.e.) with n-$BuNH_2$ or $PhNH_2$, undergo spontaneous separation into the liquid excess enantiomer and the crystalline racemic compound. The unit cell of the latter contains heteroenantiomeric pairs of molecules, bound together by strong hydrogen bonds. These observations were the basis of our assumption that similar separations might be possible in the cases of the optically active 2α-hydroxypinan-3-one **4** and even its oxime **5**.

2α-Hydroxypinan-3-one **4**, obtained from (+)-α-pinene **3** of Ca. 65% e.e., solidifies after rectification. However, attempts to fractionally crystallise this material give poor and random results. Nonetheless, we noticed that condensed (supersaturated) hexane solutions (60–70% mixtures with hexane) containing 1% v/v of ethylene glycol or triethanoloamine yield, after seeding, crystals of pure excess enantiomer, while a racemic mixture remains in solution. The process is stopped when the transparent crystals start to turn turbid. This allows the isolation of near enantiopure **4**. Condensation of the remaining solution of about 15–40% e.e., and seeding with a racemic crystal yields a crystalline fraction of the racemic compound and concomitant enantiomeric enrichment of the soluble material to 60–75% e.e. Repeating the procedure leads to near-quantitative separation of the excess enantiomer and racemic compound.

In our hands, using a slightly modified Chabudziński method, 2α-hydroxypinan-3-one of 67% e.e. yielded the oxime almost quantitatively. The crude oxime, solidifying from a condensed solution was a mixture of the racemic compound and crystals of pure excess enantiomer. The markedly different solubility of the two forms in boiling hexane (50 g/dm^3 for pure enantiomer and 3 g/dm^3 for racemate) allows their rapid and convenient separation. Extracting the excess enantiomer by repeatedly washing the mixture of solids with boiling hexane yields the soluble oxime of enantiomeric purity 90–95% from material of 67% e.e. and leaves the poorly soluble racemate. Crystallisation of the racemate from chloroform yields prisms (mp 131°C; lit. 127°C[6] and 144–146°C[9]). The near enantiopure oxime (90–95% e.e.), extracted with boiling hexane from the solidified mixture, yields, after two fractional crystallisations (hexane–ether 10:1), enantiomerically pure **5** {mp 119°C, $[\alpha]_D^{20} = +19.1$ (c 3, $CHCl_3$)}.

In order to determine the enantiomeric purity of compounds **4** and **5**, we employed the widely used chiral solvating reagent (CSA) procedure, which makes use of NMR methods for the estimation of e.e. In our case, optically active *tert*-butylphenylphosphinothioic acid was found to be the chiral solvent of choice.[10] In order to find the most convenient diagnostic signals, spectra were recorded in different solvents ($CDCl_3$, C_6D_6,) with 5–10% excess of (+)-(*R*)- or (−)-(*S*)-acid.

The signals for Hβ at C-7 of the racemic ketol: δ ($CDCl_3$) = 1.666 (d, 1H, J = 11.0 Hz), in the presence of (+)-(*R*)-*tert*-butylphenylphosphinothioic acid were separated into two doublets at δ = 1.670 and 1.656 for (+)-(2*S*)- and (−)-(2*R*)-hydroxypinan-3-one, respectively. In the same spectrum, the signal for the 10-CH_3 group in the (+)-(*S*)-keto alcohol (δ = 1.382), well separated from signals from the signals for 10-CH_3 groups of other compounds, can be very useful in finding small amounts of this enantiomer in the mixture.

In C_6D_6, the diagnostic signals are those for Hβ at C-7. C_6D_6 was found to be the best solvent for obtaining well resolved ^{1}H NMR spectra of mixtures of the (−)-(1*S*,2*S*)- and (+)-(1*R*,2*R*)-oximes **5**. The spectrum of the racemic oxime in the presence of (+)-(*R*)-*tert*-butylphenylphosphinothioic acid shows six independent signals for the methyl groups of both enantiomers. These signals are grouped into three pairs: δ; (0.4103, 0.5101 $-^9CH_3$); (0.9351, 0.9765 $-^8CH_3$); (1.5751, 16554 $-^{10}CH_3$) and in each pair, the signals of higher value come from the (+)-(1*R*,2*R*)-enantiomer of oxime.

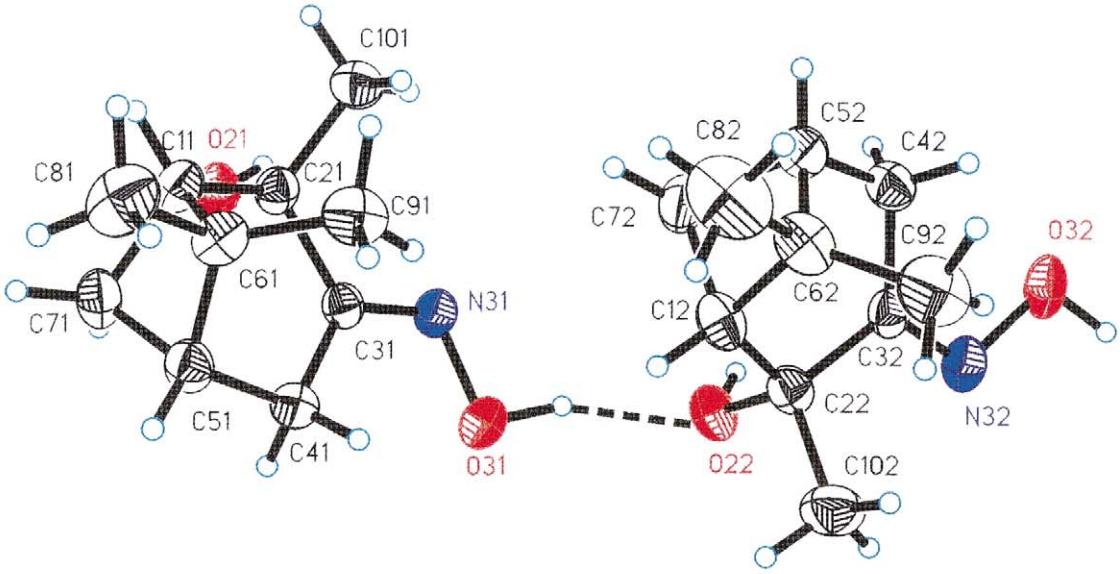
The results obtained by implementing the method described above are consistent in the range of 50–98% e.e. Levels of as little as 0.5% of the other enantiomer in the sample can be detected. It is worth mentioning that changes in chemical shifts recorded in the presence of *tert*-butylphenylphosphinothioic acid can make the interpretation of the spectrum easier. For example, signals for Hα and Hβ at C-4 have similar chemical shifts, resulting in overlapping 2H signals; while in the presence of *tert*-butylphenylphosphinothioic acid resolved signals are observed.

The ^{1}H NMR spectra of oxime **5** ($CDCl_3$) conform to the published data,[6,8] as well as to expectations regarding an *anti*-oxime, in which the coupling of the 4-CH_2 hydrogen decreases or disappears due to an electronegative oxygen atom in their vicinity. The similarity of the chemical shifts makes full interpretation of spectra impossible; however, switching the solvent to Py-d_5 separates the signals and allows determination of coupling constants between the 1-CH, 4-CHα, 4-CHβ, 5-CH, 7-CHα and 7-CHβ protons (see Section 4 part for details).

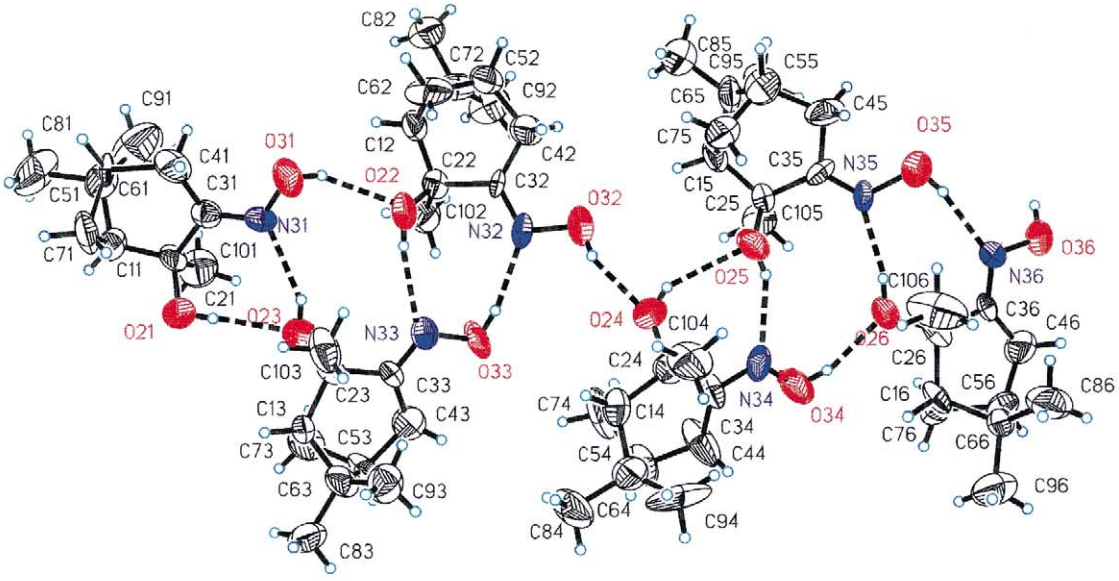
The ease of the enantiomeric purification of oxime **5** is related to the different physical properties of the crystals of the pure enantiomer and the racemic mixture. Although the molecules in the heteroenantiomeric crystals are generally more densely packed, the number of hydrogen bonds, their strength and direction are the

factors dictating the stability of the crystals. Large differences in the hydrogen bonding patterns of the pure enantiomer and racemate crystals have been validated by their crystal and molecular structures. (Fig. 2a and Fig. 3a).

Racemate monocrystals (from chloroform solution) are monoclinic prisms (mp 131°C and calculated density $D_x = 1.219$ g/cm^3). The unit cell contains two molecules (Fig. 2a). In the crystal, two distinct pairs of heteroenantiomeric dimers with different hydrogen bonding patterns were identified as the repeating elements (Fig. 3a and Table 1). Molecules defined as **2** form 12-membered rings, and follow the hydrogen bonding via O22–H22 hydroxyl groups and oxime oxygen O32 (1/2–x, $-1/2+y$, 1/2–z), while molecules **1** joined by hydrogen bonds O21–H21···N31 (1/2–x, $-1/2+y$, and 1/2–z) are arranged in a 10-membered ring. Both dimeric rings bind each other in infinite chains via two types of hydrogen bonds between the oxime hydrogens



a



b

Figure 2. ORTEP drawing of the independent molecular systems for (a) racemate; (b) pure enantiomer.

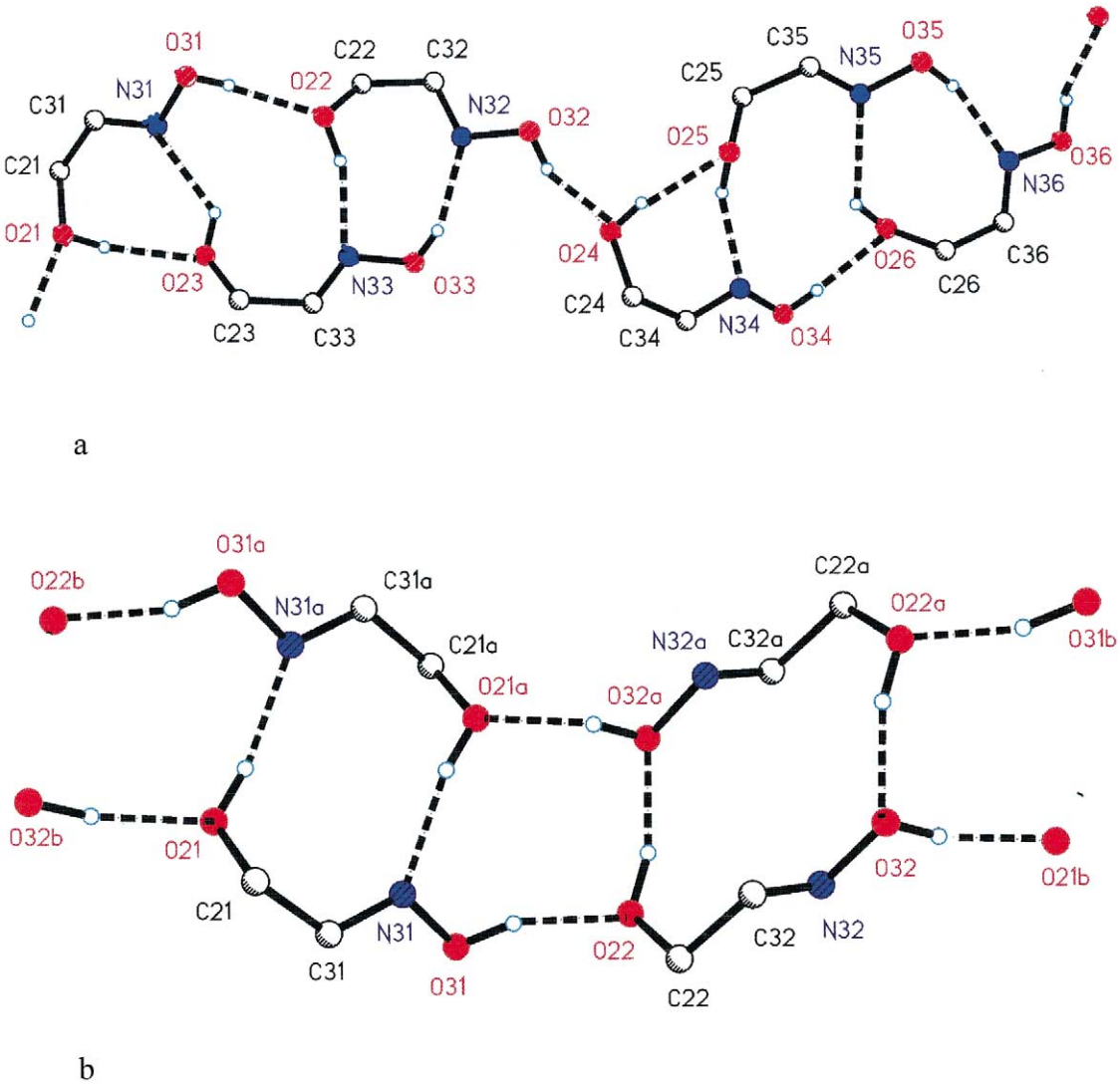


Figure 3. H-bond motions in the crystal of (a) racemate; (b) (+)-enantiomer.

Table 1. H-bond geometries

	X–H···Y (symm. cod)	X–H (Å)	H···Y (Å)	X···Y (Å)	X–H···Y (°)
Racemate	O21–H21···N31 (1/2−x, −1/2+y, 1/2−z)	0.92	1.99	2.907	169.5
	O22–H22···O32 (1/2−x, 1/2+y, 1/2−z)	0.98	1.79	2.750	163.4
	O31–H31···O22	0.98	1.81	2.758	162.5
	O32–H32···O21	0.94	1.81	2.717	161.4
Enantiomer	O23–H23···N31	0.82	2.14	2.866	148.0
	O33–H33···N32	0.82	2.02	2.823	165.2
	O22–H22···N33	0.82	2.12	2.926	165.7
	O25–H25···N34	0.82	2.14	2.885	151.2
	O26–H26···N35	0.82	2.07	2.858	162.1
	O35–H35···N36	0.82	2.03	2.823	162.0
	O21–H21···O23	0.82	2.10	2.856	153.7
	O24–H24···O25	0.82	2.23	2.893	138.3
	O31–H31···O22	0.82	2.10	2.806	145.0
	O34–H34···O26	0.82	1.94	2.736	163.1
	O32–H32···O24	0.82	1.92	2.632	145.5
	O36–H36···O21 (x, 1−y, z)	0.82	1.98	2.672	142.3

and the hydroxyl oxygens: O31–H31···O22, and O32–H32···O21. In consequence, nine-membered rings are formed. It should be emphasised that all H-bonds in the crystal are created by an even number of the molecules being different enantiomers.

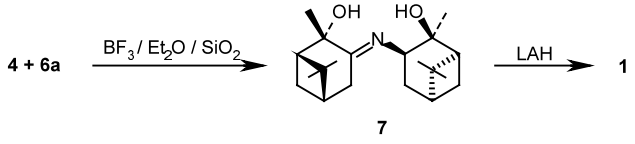
After crystallisation from hexane, the pure enantiomer gave twined simples (mp 119°C and density $D_x = 1.121$ g/cm^3). The single crystals are in the form of fine needles. It was found that six molecules are located in acentric triclinic cells. In the crystal two trimeric (odd number of the molecules) systems can be selected (Fig. 2b). Molecules in triplets **1**–**3** and **4**–**6** are connected by hydrogen bonds into 17-membered rings with two O–H···N hydrogen bonds bridges (Fig. 3b and Table 1). Two three-molecule systems within the cell are rotated with respect to each other almost at 180°, and connected with each other, as well as with the neighbouring fragment, by a single strong O–H···O (2.672 Å) hydrogen bond. This type of crystalline structure is weaker than that of the racemate, where the heteroenantiomeric dimers interact with their neighbouring molecules through two strong hydrogen bonds (2.758 and 2.717 Å).

On reduction with LAH in diethyl ether according to Chabudziński's procedure,[6] the enantiomerically pure oxime of 2α-hydroxypinan-3-one **5** affords enantiomerically pure 2α-hydroxy-3α-aminopinane **6a** (see Scheme 1).

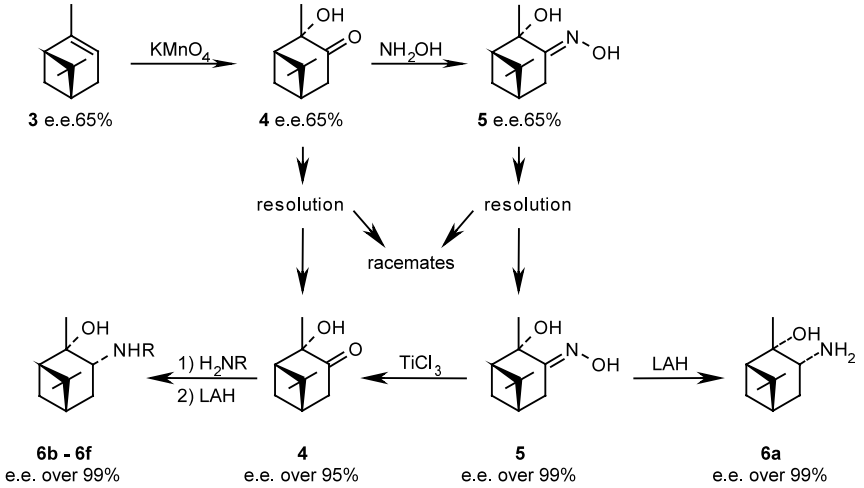
Having enantiomerically pure samples of 2α-hydroxypinan-3-one **4** and amino alcohol **6a** in hand, we decided to synthesise di[3α-(2α-hydroxypinane]amine **1** via the Schiff base. A direct application of the method utilised previously[7] (reaction of ketol **4** and hydroxyamine **6a** in toluene, with $BF_3{\cdot}Et_2O$ or *p*-toluenesulphonic acid present as a catalyst), was unsuccessful. However, a modification of this method, using $BF_3{\cdot}Et_2O$ adsorbed on silica gel as a catalyst, allowed after optimisation, a 60% turnover of substrates in 18 h. Separation of the product from non-transformed substrates by flash chromatography yielded the pure compound, crystallising in the form of prisms of mp 134–136°C and $[\alpha]_D^{20} = -95.8$ (*c* 2; $CHCl_3$). Spectroscopic data [MS: M+1 = 320; characteristic IR bands at 3460 cm^{-1} (OH), 1645 cm^{-1} (C=N), 1395 and 1390 cm^{-1} (*gem* CH_3)] confirm the structure of **7**. In ^{1}H NMR ($CDCl_3$) spectrum six single lines at δ: 0.851 (s, 3H), 1.021 (s, 3H), 1.171 (s, 3H), 1.296 (s, 3H), 1.333 (s, 3H), 1.498 (s, 3H), corresponding to six different methyl groups were observed. Other signals are also in agreement with the structure **7** (see Scheme 2 and Section 4).

Reduction of **7** with LAH in diethyl ether leads to the formation of amine **1** in 85–88% yield (crystallised from methylcyclohexane, mp 118–119°C; $[\alpha]_D^{20} = -35.5$, MS: M+1 = 322).

In the ^{1}H NMR spectrum of **1** (C_2-symmetrical di[3α-(2α-hydroxy)pinane]amine) the following signals were observed: δ: 0.974 (s, 6H, $^9CH_3$ and $^{9'}CH_3$), 1.255 (s, 6H, $^8CH_3$ and $^{8'}CH_3$), 1.270 (d, 2H, $J_{gem} = 18.1$, ^{7}CHβ and $^{7'}$CHβ), 1.300 (s, 6H, $^{10}CH_3$ and $^{10'}CH_3$), 1.503 (ddd, 2H, $J_{gem} = 13.6$, $J_{4CH\beta,3CH\beta} = 6.4$, $J_{4CH\beta,5CH} = 2.3$, ^{4}CHβ and $^{4'}$CHβ), 1.923 (m, 2H, ^{5}CH and $^{5'}$CH), 1.978 (dd, 2H, $J_{1CH,7CH\alpha} \approx J_{1CH,5CH} \approx 5.9$, ^{1}CH and $^{1'}$CH), 2.164 (m, 2H, $J_{gem} = 18.1$, $J_{7CH\alpha,1CH} \approx J_{7CH\alpha,5CH} \approx 5.9$–6.0, $J_{7CH\alpha,4CH\alpha} = 2.30$, ^{7}CHα and $^{7'}$CHα), 2.469 (m, 2H, $J_{gem} = 13.6$, $J_{4CH\alpha,3CH\beta} = 9.4$, $J_{4CH\alpha5CH} = 6.0$, $J_{4CH\alpha,7CH\alpha} = 2.3$, ^{4}CHα and $^{4'}$CHα), 3.086 (dd, 2H, $J_{3CH\beta,4CH\alpha} = 9.4$, $J_{3CH\beta,4CH\beta} = 6.4$, ^{3}CHβ and $^{3'}$CHβ); Unfortunately, the signal from ^{7}CHβ and $^{7'}$CHβ (d, 2H)



Scheme 2.



b) R = *n*-Pr, c) R = *n*-Bu, d) R = *i*-Pr, e) R = Ph, f) R = CH_2CH_2OH

Scheme 1.

is masked by the signals of the $^{8,8'}CH_3$ and $^{10,10'}CH_3$ methyl groups; however, it can be observed if a shift reagent was added. Compared to the ^1H NMR spectrum of 2α-hydroxy-3α-aminopinane, the differences in chemical shifts are only in the 0.13 ppm range ($^3CH\beta$). The ^{13}C NMR spectrum of **1** contains only ten signals, proving the C_2-symmetry.

Enantiomerically pure **6a** was successfully used by Shioiri[8] in syntheses of numerous oxazaborolidines and the reduction of prochiral ketones with BH_3 carried out in their presence, yielded respective alcohols with enantiomeric purities reaching 93–94%.

Our tests on **6a**, the earlier prepared[7] 2α-hydroxy-3α-*N*-alkyl(aryl)aminepinanes **6b–f** and C_2-symmetric **1** as the catalysts (10% mol) in the reduction of acetophenone with BH_3, proved successful, leading to good chemical yields and good or moderate enantiomeric purities of the products. Some of the results obtained are presented in Table 2.

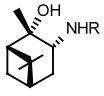
Among the several hundred publications regarding the catalytic asymmetric addition of organozinc to carbonyl compounds (latest review[12]), only five describe applications of pinane derivatives. In all of these cases (−)-β-pinene was the source of chirality. Goralski and co-workers transformed nopinone (e.e. 92%, obtained from β-pinene) into several 2β-dialkylamino-3α-hydroxypinanes.[13] In independent studies Chelucci and Soccolini,[14] and Kwong and Lee[15] investigated the 2β-hydroxy-2α-(2-pyridino)nopinanes available from nopinone and their C_2-symmetric 2,2′-bipyridinodiol analogues.

(−)-Myrtenol was the precursor of 10-*N*- or *O*-substituted 2α,3α-pinanediols of enantiomeric purity 93.8%, obtained by Lu and co-workers[16] and (−)-Myrtenal was used by the von Zelewski group in syntheses of pinanepyridines, which were successfully applied as ligands for asymmetric addition of organozinc compounds to aldehydes.[17] Extensive research on ligand systems and complexes derived from pinenes by groups in China, Italy and Switzerland is still ongoing.[18]

2α-Hydroxypinan-3-one is a convenient precursor of many 2α-hydroxy-3-amino derivatives of pinane, including previously described[7b] amino alcohols **6a–f** and C_2-symmetric amino diol **1**. The results obtained from their application in asymmetric addition of diethylzinc to benzaldehyde are presented in Table 3.

Table 2. Reduction of acetophenone with BH_3 in the presence of the chiral ligands **6 a–f** and **1**

$$PhCOCH_3 \xrightarrow[BH_3{\cdot}THF,\ 0°C]{\textbf{6a–f} \text{ or } \textbf{1}\ (10\ mol\%)} PhCH(CH_3)OH(S)$$

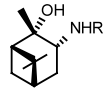
		PhCH(CH$_3$)OH			
	6a-f	% e.e.	yield [a]	% e.e. [b]	configuration
1	a. R = H	≥99	87-91	89	*S*
2	b. R = *n*-Pr	≥99	93	86-90	*S*
3	c. R = *n*-Bu	≥99	90	86	*S*
4	c. R = *n*-Bu	67	93	22	*S*
5	c. R = *n*-Bu	90	90	49	*S*
6	d. R = *i*-Pr	≥99	85	61	*S*
7	e. R = Ph	≥99	83	35	*S*
8	f. R = CH_2CH_2OH	≥99	93	41	*S*
9	**1**, R = 	>99	89	37	*S*

[a]The yield of the isolated product.

[b]The e.e. values were calculated according to the maximum specific rotation of 1-phenylethanol $\{[\alpha]_D^{25} = -45.5$ (*c* 3, MeOH)$\}$,[11a] and by GC analysis with chiral column.

Table 3. Addition reaction of Et_2Zn to benzaldehyde promoted by the ligands **6 a–f** and **1**

$$PhCHO + Et_2Zn \xrightarrow[\text{toluene, 0°C–rt}]{\textbf{6a–f or 1 (10 mol\%)}} PhCH(Et)OH(S)$$

		PhCH(Et)OH			
	6a-f	e.e. (%)	yield [a]	e.e.(%) [b]	configuration
1.	a. R = H	≥99	95 (91)	83	*S*
2.	b. R = *n*-Pr	≥99	93 (88)	89	*S*
3.	c. R = *n*-Bu	≥99	96 (89)	88	*S*
4.	c. R = *n*-Bu	67	95 (89)	11	*S*
5.	c. R = *n*-Bu	90	94 (90)	35	*S*
6.	e. R = Ph	≥99	67 (63)	43	*S*
7.	f. R = CH_2CH_2OH	≥99	96 (90)	20	*S*
8.	**1**, R = 	≥99	92 (89)	51	*S*

[a]Yield of isolated alcohol in parentheses.

[b]The e.e. values are based on the maximum specific rotation {reported value for (*S*)-1-phenylpropanol of 98% e.e. is $[\alpha]_D^{22} = -47.6$ (*c* 6.11, $CHCl_3$)},[11b] and by GC analysis on a chiral column.

Increasing the bulk of an alkyl substituent, or its exchange for an aromatic one, leads to lower enantiomeric purities. In some cases, negative direction of non-linear asymmetric induction effect was observed.[19]

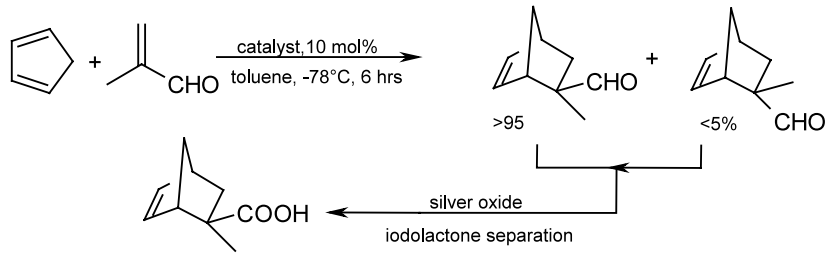
In 1979 Koga's group reported that the alkoxydichloroaluminates of menthol, isomenthol and borneol, readily obtained from reaction of the corresponding alcohols with ethyldichloroaluminum, proved to be good catalysts in the asymmetric Diels–Alder reactions of cyclopentadiene and methacrolein or acrylate.[20] It was the second (but the first effective) example of an application of optically active Lewis acids as catalysts in cycloaddition reactions. The use of chiral Lewis acids in the asymmetric catalysis of Diels–Alder reactions is well recognised. However, high enantiomeric purities were obtained only when the metal was bidentally chelated by the ligand, which limits the conformational freedom of the complex. The very high enantiomeric purities (ca. 100%) independently obtained by the Evans and Jørgensen teams in hetero Diels–Alder reactions led to these catalysts being termed 'chemzymes'.[21]

Our amino alcohols **6** and, especially, the C_2-symmetrical amino diol **1**, also present the possibility of bidentate chelation to the metal, which led us to test their application as catalytic ligands in the asymmetric Diels–Alder reaction.

Reaction of 1 mol equiv. of diethylchloroaluminum with 2 equiv. of alcohol (or 1 equiv. of diol) affords the corresponding dialkoxychloroaluminum catalyst. We tested potential catalysts, based on Et_2AlCl and the synthesised amino alcohols **6a–f** and C_2-symmetrical amino diol **1**, in the asymmetric D.A. reaction of cyclopentadiene and methacrolein. Although our attempts to separate and characterise the reaction products, especially with aminodiol **1**, failed, based on the noted evolution of ethane, we temporarily assigned structure **2** to the product from the reaction of **1** and Et_2AlCl (Scheme 3).

$$\textbf{1} + Et_2AlCl \xrightarrow{\text{toluene}} \textbf{2} + 2\ EtH$$

Scheme 3.



Scheme 4.

Amino alcohols **6b–e** induced moderate enantioselectivities when used as chiral ligands for an in situ generated catalyst in the cycloaddition of cyclopentadiene and methacrolein. C_2-Symmetrical amino diol **1**, used in 10% excess with regard to Et_2AlCl, afforded the product in 89% yield with enantiomeric purity of 76–79% (Scheme 4).

The major *exo*-adducts were purified by column chromatography (Table 4; entries 1–5),[23] or by oxidation of the mixture of aldehydes obtained to carboxylic acids, which then allows removal of the iodolactone derivative of the *endo* isomer (Table 4; entry 6).[24] In December 2001 Hiroi and Watanabe published the first example of employing a 2α-hydroxypinan-3-one derivative (imino-phosphino ligand) in the palladium-catalysed asymmetric Diels–Alder reaction.[25]

3. Conclusion

(+)-α-Pinene with low enantiomeric purity can be successfully used to prepare enantiomerically pure derivatives via 2α-hydroxypinan-3-one and its oxime. Because of their low cost, 2α-hydroxy-3α-aminopinane and its *N*-alkyl(aryl) analogues—good catalytic ligands in asymmetric BH_3 reductions and the asymmetric alkylation of aldehydes with diethylzinc—have potential for wide synthetic use. The C_2-symmetric compound **1**, tested in the above reactions, gave poor results, yielding products with enantiomeric purities of 37 and 51%, respectively. However, as we expected, as a chiral ligand for Lewis acid catalysed asymmetric Diels–Alder reaction, **1** proved useful.

4. Experimental

4.1. General

Boiling points are uncorrected. Melting points were determined on a Büchi 510 apparatus in open capillaries and are uncorrected. Elemental analyses were performed in CBMiM PAN (Łódz). Optical rotation was measured with a Horiba SEPA–200 apparatus in a 10 cm cell. IR spectra were taken with a Specord M80 spectrometer. ^1H and ^{13}C NMR spectra were recorded at 250 and 62.9 MHz, respectively, with a Bruker Avance DPX–250 apparatus in $CDCl_3$ (TMS). The values of the coupling constants are reported in Hz. (Analytical ^1H NMR spectra-Bruker 200 at 200 MHz). Mass spectra were determined with Fab MI 1201 E (P.O. Electron, Ukraine) (FAB). GC was performed with Shimadzu apparatus, using 25 m CP Chirasil Dex. CB. OF = 0.25 column. TLC was performed on silica gel 60 F_{254} aluminium plates (0.2 mm). PLC was performed on silica gel 60 F_{254} (2 mm) plates (Merck). Regular and flash column chromatography was carried out using Merck silica gel 60 (70–230 and 230–400 mesh, respectively). Acetophenone and benzaldehyde were distilled from calcium hydride under argon atmosphere prior to use. Diethyl ether and tetrahydrofurane were distilled from sodium and benzophenone prior to use. Dichloromethane was dried over calcium hydride and distilled before use. Other solvents were dried and purified using standard procedures.

4.2. (−)-2α-Hydroxypinan-3 one, 4

Compound **4** was synthesised from (+)-α-pinene (>98%, GC) obtained from Polish wild pine (*Pinus silvestris*) turpentine by fractional distillation; $\alpha_D^{20} = +34.1°$ (neat), e.e. = 65% [commercial Polish (+)-α-pinene concentrate 92–95% (GC) was also used on 5 mol scale], according to the procedure of Carlson and Pierce.[3a] The crude ketol was purified by rectification with 1 m column; chemical purity >98% (GC), $n_D^{20} = 1.4895$ (overcooled liquid), $[\alpha]_D^{20} = -25.9$ (*c* 0.5, $CHCl_3$). Yield 42–45%.

4.3. Enantiomeric purification of ketol 4

Rectified ketol (84 g) was melted with hexane (60 ml) and ethylene glycol (1.0 g). After cooling the mixture to 4°C, it was nucleated with a crystal of enantiomerically pure ketol and left at that temperature. After 36 h, as the surface of emerging crystals started to become turbid, they were filtered and washed with cold hexane (30 ml) to afford crystalline product (44.5 g), mp = 31–34°C, $[\alpha]_D^{20} = -38.0$ (*c* 0.5, $CHCl_3$) was obtained. Further crystallisation from hexane (60 ml) afforded 41 g of compound with mp = 36–38°C, $[\alpha]_D^{20} = -39.5$ (*c* 0.5, $CHCl_3$) and e.e. >98%, as determined by ^1H NMR analysis.

The hexane fractions were combined and washed with water (2×50 ml) in order to remove glycol, dried over magnesium sulphate. The solvent was evaporated in vacuum, yielding pale yellow oil (42.6 g); $[\alpha]_D^{20} = -12.5$ (*c* 0.5, $CHCl_3$). The oil was melted hexane (30 ml) and ethylene glycol (0.5 g). After cooling the mixture down to 4°C it was nucleated with racemate and left at that temperature. After 3 days 21.7 g of crystals were obtained: mp = 30–31°C, $[\alpha]_D^{20} = -0.9$ (*c* 0.5, $CHCl_3$).

The above experiment was carried out a number of times, using from 0.1 to 2 mol of ketol, with comparable chemical and enantiomeric purities of all fractions (±10%).

4.4. Oximation of ketol 4, and enantiomeric purification of oxime 5

A sample of rectified ketol (84 g), $[\alpha]_D^{20}=-25.9$ (*c* 0.5, $CHCl_3$), was dissolved in ethanol (250 ml), then a solution of $NH_2OH\cdot HCl$ (51 g) and $AcONa\cdot 3H_2O$ (103 g) in water (70 ml) was added. The reaction mixture, after mixing in a shaker for 6 days at room temperature, was diluted with water (200 ml), ethanol evaporated under reduced pressure (<35°C) and the residue extracted with $CHCl_3$ (3×200 ml). The combined extracts were washed with water (4×200 ml), dried over magnesium sulphate and concentrated in vacuo. Colourless or pale yellow product (containing 3–5% $CHCl_3$) solidified after 1–2 days at −18°C. After crushing the solid and washing it with cold hexane (50 ml), the solvents were evaporated, and the crude oxime (91 g, 99%) was obtained; $[\alpha]_D^{20}=+12.3$ (*c* 3, $CHCl_3$), e.e.= 65% (determined also by ^{1}H NMR).

The crude oxime (91 g) was extracted by heating under reflux in hexane (700 ml) for 15 min. This procedure was repeated three times The combined hexane extracts crystallised on cooling to room temperature. The mixture was filtered to afford the crystalline oxime (56.1 g) mp 116°C, $[\alpha]_D^{20}=+17.4$ (*c* 3, $CHCl_3$). The mother liquor yielded after condensation, a further 9 g of oxime of $[\alpha]_D^{20}=+13.5$ (*c* 3, $CHCl_3$), (e.e. 92% and 70%, respectively). The yellow oily residue (1 g) contained mostly the oxime. Crystallisation of oxime of $[\alpha]_D^{20}=+17.4$ from a mixture of diethyl ether–hexane (1:10) afforded a product with $[\alpha]_D^{20}=+18.5$, and recrystallisation afforded the enantiomerically pure oxime **5** in the form of needles: mp 119°C, $[\alpha]_D^{20}=+19.1$ (*c* 3, $CHCl_3$), e.e. >99% (determined by ^{1}H NMR); $IR_{(KBr)}$, cm^{-1}; 3300 (OH), 960 (=NOH). ^{1}H NMR δ: 0.86 (s, 3H, $^9CH_3$), 1.30 (s, 3H, $^8CH_3$), 1.55 (s, 3H, $^{10}CH_3$), 1.59 (d, 1H, ^{7}CHβ, $J_{gem}=10.6$), 2.00 (m, 2H, ^{1}CH and $^7CH_\alpha$), 2.32 (m, 1H, ^{5}CH), 2.73 (m, 2H, $^4CH_2$), 3.35 (1H, OH), 9.00 (1H, =NOH), ^{13}C NMR; 22.32 (^{9}C), 27.17 (^{8}C), 27.86 (^{7}C), 27.97 (^{10}C), 29.94 (^{4}C), 37.43 (^{5}C), 38.62 (^{6}C), 51.30 (^{1}C), 163.09 (^{3}C).

The oxime insoluble in hexane (26.2 g) was racemate. Crystallisation from chloroform yielded prisms of mp= 131°C. IR, ^{1}H NMR identical with pure enantiomer, 1H NMR (Py-d_5, TMS) δ: 0.919 (s, 3H, $^9CH_3$), 1.249 (s, 3H, $^8CH_3$), 1.892 (s, 3H, $^{10}CH_3$), 1.952 (sept, 1H, $J_{5CH,1CH}\approx J_{5CH,7CH\alpha}\approx 5{,}8\sim 6.0$, $J_{5CH,4CH\alpha}=2.5$, $J_{5CH,4CH\beta}=3.0$, ^{5}CH), 2.080 (d, 1H, $J_{gem}=10.3$, $^7CH_\alpha$), 2.203 (dd, 1H, $J_{5CH,1CH}\approx J_{1CH,7CH\alpha}=5.8$–6.0, ^{1}CH), 2.362 (m, 1H, $J_{gem}=10.3$, $J_{7CH\alpha,1CH}\approx J_{7CH\alpha,5CH}=5.8$–6.0, $J_{7CH\alpha,4CH}=3.0$, ^{7}CHα), 2.943 (dd, 1H, $J_{gem}=18.5$, $J_{4CH\beta,5CH}=2.5$, ^{4}CHβ), 3.185 (ddd, 1H, $J_{gem}=18.5$, $J_{4CH\alpha,5CH}=2.5$, $J_{4CH\alpha,7CH\alpha}=3.0$, ^{4}CHα).

Total yield from over ten experiments carried out in the range of 5–168 g of used ketol **4**, calculated as the sum of enantiomerically pure and racemic crystalline oxime, was 93%.

4.5. X-Ray structure analyses

4.5.1. Crystal data for racemate. $C_{10}H_{17}NO_2$, $M=$ 183.25, monoclinic, space group $P2_1/n$, $a=12.578(3)$, $b=11.753(2)$, $c=13.610(3)$ Å, $\beta=97.07(3)°$, $V=$ 1996.7(7) Å^3, $Z=8$, $D_x=1.219$ g/cm^3, $T=297$ K, $\mu=$ 0.678 mm^{-1}, $\lambda=1.54178$ Å, $F(000)=800$, colourless prisms (0.3×0.3×0.3 mm). Data collected on KM-4 diffractometer and monochromated Cu Kα radiation with ω–2θ scan mode, $\theta_{max}=80°$. Correction for absorption was not applied. Structure solution by direct methods, refinement by full-matrix least squares on F^2, data/parameters=4358/236; final $R_1=0.0366$, $wR_2=$ 0.1040 (all data). Crystallographic data (excluding structural factors) for the structure have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 181871.

4.5.2. Crystal data for enantiomer. $C_{10}H_{17}NO_2$, $M=$ 183.25, triclinic, space group P1, $a=7.2110(10)$, $b=$ 12.917(3), $c=17.971(4)$ Å, $\alpha=87.15(3)$, $\beta=81.64(3)$, $\gamma=79.70(3)°$, $V=1628.9(6)$ Å^3, $Z=6$, $D_x=1.121$ g/cm^3, $T=297$ K, $\mu=0.08$ mm^{-1}, $\lambda=0.71073$ Å, $F(000)=600$, colourless needles (0.05×0.05×0.5 mm). Data collected on KM-4 diffractometer with a CCD detector and monochromated Mo Kα radiation with ω-scan mode, $\theta_{max}=36°$. Correction for absorption was not applied, absolute structure known from chemistry. Structure solution by direct methods, refinement by full-matrix least squares on F^2 (SHELXl-93).[26] Data/parameters= 3994/670; final $R_1=0.0975$, $wR_2=0.2448$ (all data). Crystallographic data (excluding structural factors) for the structure have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 181870.

4.6. (1*S*,2*S*,3*R*,5*S*)-3-Amino-2-hydroxypinane, 6a

Amino alcohol **6a** was obtained by reduction of enantiomerically pure oxime **5** with LAH, according to the procedure of Chabudziński[6] at 0.05 and 0.2 mol scale. After recrystallisation from hexane/ether: mp 45–47°C, $[\alpha]_D^{20}=-14.1$ (*c* 1, $CHCl_3$). Spectral data (IR, ^{1}H NMR) were identical to that reported.[8]

4.7. Schiff base 7

A 250 ml flask equipped with a magnetic stirring bar and Dean–Stark apparatus was charged under argon with toluene (120 ml), silica gel (2 g) and $BF_3\cdot Et_2O$ (0.5 ml). After stirring the mixture for 15 min at room temperature, enantiomerically pure amino alcohol **6**a (5.0 g, 0.0295 mol) and 2α-hydroxypinan-3-one (5.0 g, 0.0295 mol) were added. The mixture was heated under reflux for 6 h and the water collected in Dean–Stark apparatus. After cooling, a suspension of silica gel (1 g) and three drops of $BF_3\cdot Et_2O$ in toluene (30 ml) was added and heating continued for 10 h. Filtration of silica gel and removal of solvent in vacuo afforded 9.9 g of yellow oil. Purification by chromatography column

yielded pure **7** (6.9 g (70%) of. $R_f = 0.11$ (hexane:ethyl acetate = 3:1), mp 134–136°C (crystallised from hexane), $[\alpha]_D^{20} = -95.9$ (*c* 2, $CHCl_3$). MS, M+1 = 321, M+23 = 342, IR_{KBr} 3460 (OH), 1645 (OH), 1395 and 1390 (*gem* CH_3); ^1H NMR, δ: 0.851 (s, 3H), 1.021 (s, 3H), 1.171 (s, 3H), 1.296 (s, 3H), 1.333 (s, 3H), 1.498 (s, 3H), 1.520 (d, 1H), 1.622 (d, 1H), 1.920 (m, 1H), 2.032–2.111 (m, 3H), 2.219 (m, 1H), 2.327–2429 (m, 2H), 2.504 (m, 1H), 2.545 (m, 1H), 2.710 (dd, 1H), 3.652 (dd, 1H).

4.8. Di[3α-(2α-hydroxy)pinane]amine, 1

To a vigorously stirred suspension of LAH (1.5 g, 0.037 mol) in ether (200 ml), a solution of Schiff base **5** (4.0 g, 0.0125 mol) in ether (50 ml) was added dropwise at boiling temperature. The mixture was heated under reflux for 15 h, and the complexes decomposed by addition of water (100 ml). The layers were separated, and the aqueous phase was washed with ether (2×100 ml). Mixed ether extracts were washed with brine (3× 100 ml) and dried over $MgSO_4$. The solvent was evaporated, and the solid residue recrystallised from hexane. 3.8 g (95%), mp 118°C, $[\alpha]_D^{20} = -35.5$ (*c* 2, $CHCl_3$), MS: M+1 = 323.; IR (KBr) cm^{-1}: 3320, 1650, 1385 and 1370; ^1H NMR δ: 0.974 (s, 6H, $^9CH_3$ and $^{9'}CH_3$), 1.255 (s, 6H, $^8CH_3$ and $^{8'}CH_3$), 1.270 (d, 2H, $J_{gem} = 18.1$, $^7CH\beta$ and $^{7'}CH\beta$), 1.300 (s, 6H, $^{10}CH_3$ and $^{10'}CH_3$), 1.503 (ddd, 2H, $J_{gem} = 13.6$, $J_{4CH\beta,3CH\beta} = 6.4$, $J_{4CH\beta,5CH} = 2.3$, $^4CH\beta$ and $^{4'}CH\beta$), 1.923 (m, 2H, ^5CH and $^{5'}CH$), 1.978 (dd, 2H, $J_{1CH,7CH\alpha} \approx J_{1CH,5CH} \approx 5.9$, ^1CH and $^{1'}CH$), 2.164 (m, 2H, $J_{gem} = 18.1$, $J_{7CH\alpha,1CH} \approx J_{7CH\alpha,5CH} \approx 5{,}9$–6.0, $J_{7CH\alpha,4CH\alpha} = 2.30$, $^7CH\alpha$ and $^{7'}CH\alpha$), 2.469 (m, 2H, $J_{gem} = 13.6$, $J_{4CH\alpha,3CH\beta} = 9.4$, $J_{4CH\alpha5CH} = 6.0$, $J_{4CH\alpha,7CH\alpha} = 2.3$, $^4CH\alpha$ and $^{4'}CH\alpha$), 3.086 (dd, 2H, $J_{3CH\beta,4CH\alpha} = 9.4$, $J_{3CH\beta,4CH\beta} = 6.4$, $^3CH\beta$ and $^{3'}CH\beta$); ^{13}C NMR δ: 23.932 (^9C and $^{9'}C$), 27.957 (^8C and $^{8'}C$), 28.365 (^4C and $^{4'}C$), 30.883 (^{10}C and $^{10'}C$), 37.587 (^7C and $^{7'}C$), 38.469 (^6C and $^{6'}C$), 40.563 (^1C and $^{1'}C$), 54.551(^5C and $^{5'}C$), 56.550 (^3C and $^{3'}C$), 73.125 (^2C and $^{2'}C$). Anal. calcd for $C_{20}H_{35}NO_2$: C, 74.72; H, 10.97; N, 4.36. Found C, 74,63; H, 11.05; N, 4.27%.

4.9. Typical procedure for asymmetric reduction of acetophenone

A 250 ml flask, equipped with a magnetic stirring bar, was charged under argon with amino alcohol **6a–f** or aminodiol **1** (0.00125 mol) and THF (50 ml). 1 M solution of BH_3·THF (12.5 ml) was added via syringe. After stirring at room temperature for 30 min, the mixture was cooled to 0°C, and a solution of acetophenone (1.50 g, 0.0125 mol) in THF (20 ml) was added dropwise over 1 h. After stirring for 6 h at 0°C, a mixture of water (1 ml) and methanol (1 ml) in THF (5 ml) was added, followed by 2 N aqueous HCl (15 ml). The solvents were evaporated in vacuo, the residue dissolved in ether (100 ml), washed with brine (3×50 ml) and dried over $MgSO_4$. Removal of the solvent afforded spectrally pure (^1H NMR) phenylmethylcarbinol. The ratio of enantiomers was determined by GC analysis. Product was distilled before optical rotation measurements. Results are summarised in Table 2.

4.10. Typical procedure for asymmetric addition of Et_2Zn to benzaldehyde

To a solution of chiral amino alcohol, **6a–f** or **1** (1.3 mmol) in toluene (14 ml), a solution of Et_2Zn (27 ml, 1 M in hexane solution) was added dropwise at 0°C. After stirring for 20 min, benzaldehyde (136 mg, 13 mmol) was added with syringe at 0°C, and the reaction was stirred for 6 h at 0°C and for 15 h at room temperature. The reaction mixture was quenched by addition of aqueous HCl solution (5%) and the mixture was extracted with ether (5×20 ml). The combined organic extracts were washed with brine (2×20 ml) and dried (Na_2SO_4). The solvents were evaporated under reduced pressure to give an oily residue. The residue was purified by preparative silica gel TLC to give optically active 1-phenylpropan-1-ol. Results are summarised in Table 3. Entries 1, 3 and 8 were repeated on 100 mmol scale, using column chromatography for purification.

4.11. Catalyst for Diels–Alder's reactions

Amino alcohol **6b–e** (2.05 equiv.), or amino diol **1** (1.05 equiv.) was added to a 100 ml flask under argon dissolved in toluene (50 ml) and cooled to −50°C. Et_2AlCl (1 M solution in hexane, 1 equiv.) was added dropwise and the catalyst allowed to form by stirring at this temperature for 3 h and cooling to −78°C.

4.12. Asymmetric cycloaddition of methacrolein to cyclopentadiene, typical procedure

A solution of freshly distilled methacrolein (0.700 g,

Table 4. Diels–Alder reaction between methacrolein and cyclopentadiene at −78°C

Entry	Catalytic ligand	Product			
		Isolated yield	$[\alpha]_D^{20}$ (*c* 1, 95% EtOH)	E.e. (%)	Configuration
1	**6b**	93[a]	+12.1[a]	52	R
2	**6c**	90[a]	+14.9[a]	64	*R*
3	**6d**	83[a]	+14.2[a]	61	*R*
4	**6e**	91[a]	+15.6[a]	67	*R*
5	**1**	86–89[a]	+17.7–18.4[a]	76–79	*R*
6	**1**	78[b]	+54.7[b]	81	*R*

[a] Aldehyde, enantiomerically pure, $[\alpha]_D^{20} = +23.3$ (*c* 1, 95% EtOH).[22]
[b] Acids, 0.03 mol scale, enantiomerically pure, $[\alpha]_D^{20} = +67.6$ (*c* 1, 95% EtOH).[22]

0.01 mol) in toluene (5 ml) was added via syringe, at −78°C, to the catalyst prepared in situ (0.001 mol). After 1 h, a solution of cyclopentadiene (1.65 g, 0.015 mol) in toluene (15 ml) was added by syringe over 1 h. The reaction mixture was stirred at this temperature for a further 6 h, then water (5 ml) was added. The aqueous layer was separated and extracted with hexane (2×20 ml). The combined organic layers washed by 1N HCl and brine (50 ml) were dried over $MgSO_4$, and the solvents were removed under reduced pressure. The resulting crude oily product was identified by ^{1}H NMR as the mixture of 2-*endo*-methyl-2-*exo*-carboaldehyde-norbornene (>95%) and its 2-exomethyl isomer. The major isomer was isolated by the following column chromatography (hexane:ether = 9:1). Configuration and e.e. were determined by correlation with enantiomerically pure compound {$[\alpha]_D^{20} = +23.3$ (*c* 1, 95% ethanol)[20,22]}. The results are summarised in Table 4.

The crude product with ligand **1**, obtained as described above, at 0.03 mol scale, was subjected to silver oxide oxidation[23] and iodolactone separation.[24] The obtained acid, {3.23 g, 71%), mp 35–38°C, $[\alpha]_D^{20} = +52.1$ (*c* 1; 95% ethanol)} had e.e. = 81%.[22]

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