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A New Class of Chiral Modifiers for the Enantioselective Hydrogenation of α-Ketoesters with Pt/Al_2O_3

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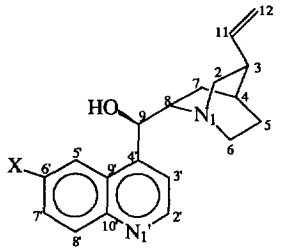
Abstract: A series of enantiomerically pure chiral amino alcohols have been synthesized and applied as modifiers in the enantioselective hydrogenation of ethyl pyruvate over supported Pt catalysts. Their use enabled an enantiomeric excess of up to 75 %. A molecular modelling study of the modifiers and reactant on a Pt (111) surface provides a possible explanation for the observed enantiodifferentiation.

In order to render a heterogeneous catalyst capable of achieving enantioselective reactions, one possibility is to introduce a chiral compound, termed a *modifier* into the reaction system. This concept has been successfully applied in two cases using natural products as modifiers: tartrate modified nickel catalysts and cinchona alkaloid modified platinum catalysts for the enantioselective hydrogenation of β-ketoesters[1] and α-ketoesters[2], respectively. The Pt/cinchona system has been studied extensively by Orito[2], Blaser[3], Baiker[4], Wells[5] and Augustine[6] and coworkers. The reaction conditions typically involve hydrogenation of either methyl or ethyl pyruvate by a cinchona alkaloid-modified supported Pt catalyst in a suitable solvent (toluene, ethanol or acetic acid for example) at 298 K and 10-70 bar hydrogen pressure. When cinchonidine or quinine (Scheme 1) is chosen as modifier, *R*-(+)-lactate is formed in enantiomeric excess, the use of the near-enantiomers cinchonine or quinidine affords of *S*-(-)-lactate as the major enantiomer.

We have recently found that structurally simple amino alcohols can substitute the cinchona alkaloids in this reaction[7]. Herein we report an extension of this work, including systematic variation of the modifier structure and molecular modelling studies of postulated modifier-reactant complexes adsorbed on the Pt surface. Our results allow a more precise definition of the structural requirements for the modifier and contribute to a better understanding of the mechanism of enantioselection.

Scheme 1



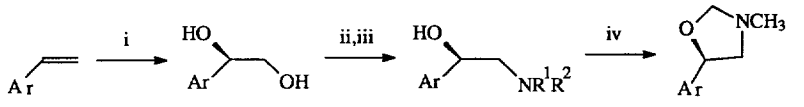
Compound	Configuration C(8)	Configuration C(9)	X
Cinchonidine	*S*	*R*	H
Cinchonine	*R*	*S*	H
Quinidine	*R*	*S*	OMe
Quinine	*S*	*R*	OMe

Several models for the function of the cinchona alkaloids in the enantioselection process have been proposed (for a comparison of these models, see ref. 8). The first mechanism[5] to describe the observed enantiodifferentiation was based on the ordered adsorption of cinchonidine with the quinoline ring parallel to the Pt surface, forming a chiral array of molecules with L-shaped cavities in between. A perpendicular adsorption of the quinoline ring of cinchonidine through the N atom and a 1:1 interaction between reactant and modifier resulting in the formation of a six-membered ring intermediate (involving both the quinuclidine N and the hydroxyl O atoms as electron donors to the carbonyl C atoms of pyruvate) was assumed later[6]. Recently, the structure of a possible intermediate, a complex formed between protonated cinchonidine and methyl pyruvate was calculated using *ab initio* and semiempirical techniques[9]. The calculations indicated that protonated cinchonidine is likely to interact with the reactant through hydrogen bonding between the quinuclidinium system and the keto group of pyruvate. This complex could easily adsorb on a flat Pt surface and be hydrogenated to form *R*-(+)-lactate. An alternative complex which would afford the opposite enantiomeric product on hydrogenation, was found to be higher in energy and less likely to adsorb on the Pt surface due to steric hindrance.

SYNTHESIS OF CHIRAL MODIFIERS

Enantiomerically pure 2-hydroxy-2-arylethylamines **4** were readily prepared from the corresponding olefins **1**, using the three-step sequence shown in Scheme 2. Sharpless asymmetric dihydroxylation[10] of **1** afforded the corresponding diols **2** in 75-85% yield and 95-98.5% ee, which could be converted to enantiomerically pure compounds by recrystallisation (>99.5% ee)[11]. Selective tosylation of the primary hydroxyl group (50-80% yield) and subsequent nucleophilic amination (60-90% yield) led to the desired amino alcohols **4**. Modifier **4i** was further converted to the oxazolidine **5** by refluxing with paraformaldehyde in toluene (70% yield).

Scheme 2



1 2 4 5

Ar = 1-naphthyl

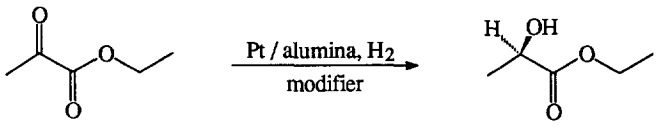
(i) AD-mix-β, H_2O/*t*-BuOH, 0 °C.
(ii) TsCl, NEt_3, CH_2Cl_2, 0 °C.
(iii) HNR_2, 25-110 °C.
(iv) $(CH_2O)_3$, toluene, 110 °C.

a	Ar= 1-naphthyl	R^1, R^2= -$(CH_2)_4$-
b	Ar= 4-quinolyl	R^1, R^2= -$(CH_2)_4$-
c	Ar= phenyl	R^1, R^2= -$(CH_2)_4$-
d	Ar= 4-pyridyl	R^1, R^2= -$(CH_2)_4$-
e	Ar= 2-naphthyl	R^1, R^2= -$(CH_2)_4$-
f	Ar= 1-naphthyl	R^1= R^2= Me
g	Ar= 1-naphthyl	R^1= R^2= ^{i}Bu
h	Ar= 1-naphthyl	R^1, R^2= -$(CH_2CH_2)_2O$
i	Ar= 1-naphthyl	R^1= H, R^2= Me
j	Ar= 1-naphthyl	R^1= H, R^2= (*S*)-CH(CH_3)Ph
k	Ar= 1-naphthyl	R^1= H, R^2= (*R*)-CH(CH_3)Ph

CATALYTIC RESULTS AND MOLECULAR MODELLING

The enantioselectivities and conversions observed when each of these chiral amino alcohols was used as modifier for the enantioselective hydrogenation of ethyl pyruvate to ethyl lactate at various pressures are reported in Table 1. The results obtained with 10,11-dihydrocinchonidine under identical conditions are also given for comparison. The kinetics of the reaction using **4a** are presented elsewhere[12]. Modifier **4a** gave the best enantiomeric excess (ee) of 68 % at 1 bar pressure (75 % ee under optimised conditions[12]), which is comparable to that achievable under similar conditions using cinchonidine as modifier (73-87 %). However, the enantioselectivity decreases with increasing hydrogen pressure, in contrast to the cinchonidine modified reaction[13] which affords the highest ee at ca. 70 bar. Hydrogenation of the naphtalene ring at the 5',6',7' and 8' positions at elevated pressures is related to this decrease in enantioselectivity[12]. Reduced ee in reaction product has also been observed when 5,6,7,8,10,11-hexahydrocinchonidine was used as a modifier[14].

Table 1: Enantioselective hydrogenation of ethyl pyruvate to (*R*)-(+)-ethyl lactate.



Modifier	H_2 Pressure / bar	Time / h	Conversion / %	ee / %
dhc[a]	1	1	100	73
	75	0.5	100	87
4a	1	1.0	100	68
	25	1.0	99	47
	75	0.5	100	46
4b	1	1.0	100	48
	25	0.5	98	55
	75	0.5	100	66
4c	25	2.0	50	0
	75	1.0	40	4
4d	1	4.0	100	0
	25	1.0	22	0
	75	1.0	30	0
4e	1	2.0	79	42
	25	2.0	34	21
	75	1.0	44	28
4f	1	2.0	95	62
	25	1.0	88	49
	75	1.0	86	45
4g	1	1.0	61	49
4h	75	0.5	98	32
4i	1	1.0	87	48
	25	1.0	88	28
	75	1.0	85	31
4j	75	1.0	33	8
4k	25	1.0	100	32
	75	0.5	100	28
5	1	2.0	53	34-44
	25	1.0	80	32-53
	75	1.0	89	49

[a] 10,11-dihydrocinchonidine.

Modifier 4b which, like cinchonidine, possesses a quinoline ring affords higher ee's with increasing hydrogen pressure. This is an indication of increased resistance to reduction afforded by the heteroatom in the aromatic ring. However, no explanation as to why either cinchonidine modified reaction or now **4b** modified reaction should have such a pressure effect has been proposed.

The reasons as to why **4a** is such an effective modifier become apparent when it is subjected to a molecular modelling study. Although many minimum energy conformations, all within a few kcal mol^{-1} of each other exist, the global minimum energy conformation is similar to that found by X-ray crystallography for cinchonidine[15]. The quinuclidine nitrogen of cinchonidine is protonated in acetic acid, the best solvent for the reaction[16]. *Ab initio* calculations found an ammonium cation-pyruvate complex (used as a model case) to be energetically more feasible than when the unprotonated ammonia molecule was used[9]. Modelling of **4a** when protonated, complexed with methyl pyruvate and energy minimised, results in the adduct depicted in Fig. 1. The complex is stabilised by a hydrogen bond between the protonated nitrogen and the α-carbonyl oxygen, similar to that calculated for a complex formed between protonated cinchonidine and methyl pyruvate[9], as shown in Fig. 2. Although ethyl pyruvate is used as a reactant, methyl pyruvate is modelled for reasons of simplicity (experimental results for both reactants are similar[3-5]).

The calculated complex would adsorb (or be formed) on a Pt surface (Pt {111} is used as an example) to present the enantioface of the pyruvate which would produce *R*-(+)-lactate on hydrogenation, assuming H transfer from the Pt surface to the adsorbed face of the keto group. In Fig. 3a the complex of **4a** and methyl pyruvate has been positioned relative to the Pt atoms. It is reasonable to expect that the aromatic rings would adsorb parallel to the surface[17] over two adjacent Pt atoms and the pyruvate would adsorb on two adjacent Pt atoms through the π-bonds of the carbonyl groups, in an analogous fashion to that proposed for alka-1,3-diene adsorption[18]. When the calculated complex is positioned as a whole, all of these adsorption criteria are *nearly* achieved. A slight repositioning of the two molecules relative to one and other, and the Pt surface would not increase the potential energy to a considerable extent. Although metal-adsorbate interactions are very important, they can not (as yet) be calculated. Therefore, the following molecular model is presented without calculation, using Pt atoms as a reference point to locate the adsorbing molecules.

If it is attempted to adsorb the other enantioface of the pyruvate to the surface, to yield S-(-)-lactate on hydrogenation, whilst maintaining the hydrogen bond, and the carbonyl groups and aromatic rings adsorbed over the Pt atoms (Fig. 3b), steric hindrance results, as observed when pyruvate and cinchonidine were modelled[19], offering an explanation as to why the interaction depicted in Fig. 3a is more favourable.

Zero to negligible ee's are achieved when the aromatic ring consists of a phenyl (**4c**) or pyridyl ring (**4d**). This can be explained in terms of the lack of any steric hindrance to adsorption of the pyruvate to yield either R-(+)- or S-(-)-lactate. Moreover, as the adsorbed modifier would be able to rotate about its site of adsorption, this increased flexibility, (less likely for a naphthalene or quinoline ring) could further decrease any steric hindrance.

Modifier **4e** is interesting as, just changing the point of attachment of the pyrrolidinyl-ethanol moiety to the naphthalene ring by one position diminishes the ee as the amount of steric hindrance to S-(-)-lactate formation is decreased.

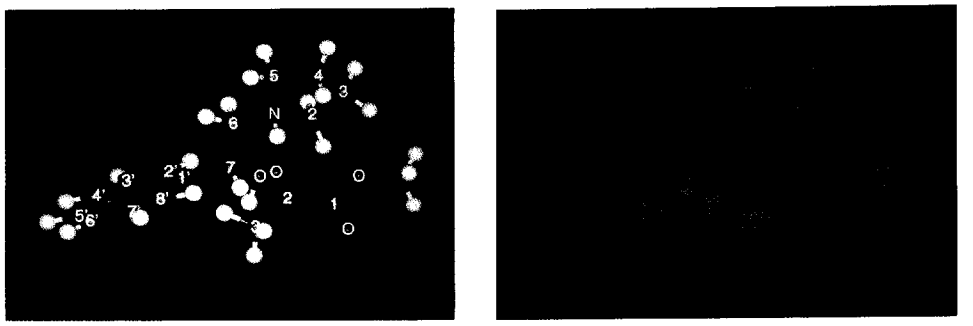
Modifier **4f** does not have a rigid ring system around the nitrogen atom which is contrary to that found in cinchonidine and **4a**. However, the ee's observed are only slightly less than when **4a** is used as a modifier, indicating that the ring system is not required, although it may be beneficial. Modifiers **4g** and **4h** also produce a lower ee in reaction product. The accessibility of the nitrogen is reduced in **4g** and **4h** by substituting two isobutyl groups on the N, or having it part of a 6-membered ring system, respectively. The reduced accessibility of the nitrogen in these modifiers, when compared to cinchonidine and **4a**, could be a possible explanation for the difference. On the other hand, **4i**, **4j** and **4k** have greater accessibility to the nitrogen, but afford lower ee's when used as modifiers. However, because they are also secondary amines, direct comparison with the other modifiers is not possible.

Moderate enantioselectivities were observed when **5** was used as a modifier. The global minimum energy conformation was such that adsorption of the aromatic ring parallel to the surface would be slightly hindered by the oxazolidine ring. Also the position of the nitrogen atom is such that the amount of steric hindrance to pyruvate adsorption, afforded by the naphthalene ring would be reduced. The reduced enantiodifferentiation can again be explained in the same manner as above.

The observed enantioselectivities shown in Table 1 provide evidence against the mechanism suggested by Augustine *et al.*[6]. The efficiencies of **4a** and **4b** are in the same range, though only the latter possesses the aromatic N atom to which a crucial role has been attributed in the mode of adsorption. Naphthalene is expected to adsorb horizontally on a flat Pt surface[17]. According to Augustine's model, a horizontal adsorption of the modifier would result in S-lactate, instead of R-lactate.

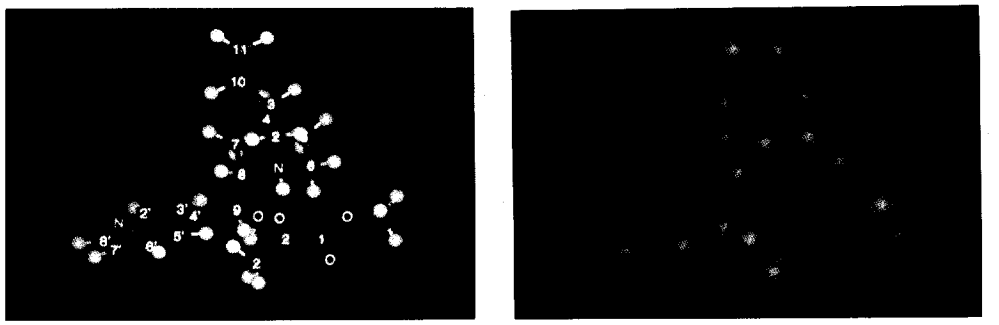
CONCLUSION

The structurally simple chiral amino alcohols **4a**, **4b** and **4f** are efficient modifiers inducing substantial enantiomeric excesses in the Pt-catalysed hydrogenation of ethyl pyruvate. At low pressure, the observed enantioselectivities rival those obtained with cinchonidine or dihydrocinchonidine, while at high pressure the alkaloid is more effective. An extended aromatic ring system such as naphthalene or quinoline, which adsorb on the Pt surface with their π-face, and a sterically accessible tertiary amino group capable of interacting with the reactant, are essential for the function of the modifier. Molecular modelling studies indicate that the conformational properties of these modifiers resemble those of cinchona alkaloids. Assuming a hydrogen bond between the protonated amino group of the modifier and the pyruvate keto group, the observed enantioselectivities can be explained in a similar way as for the Pt/cinchinidine system.



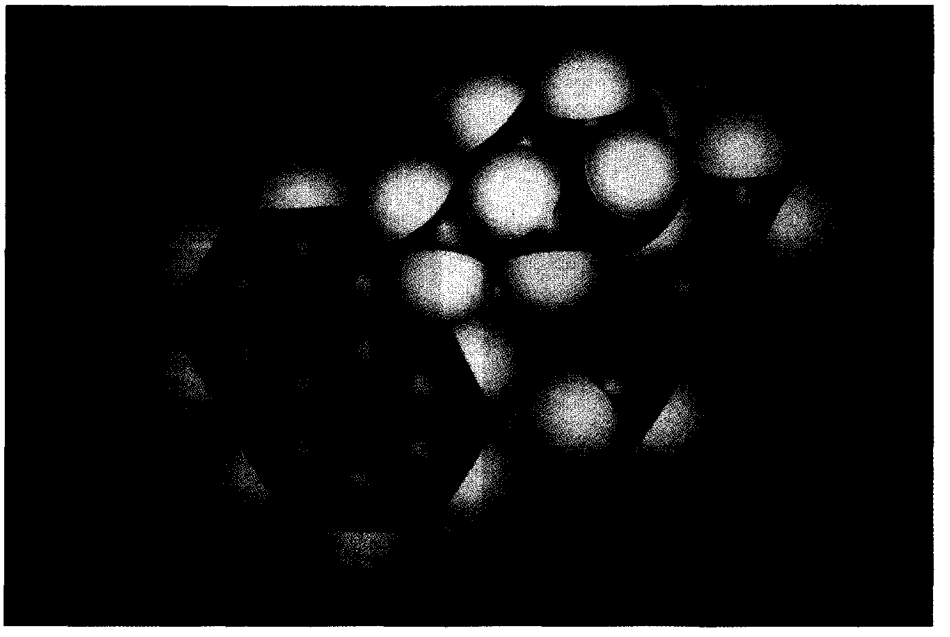
a b

Fig. 1: Calculated minimum energy conformation for the protonated **4a**-methyl pyruvate adduct; a - ball and stick model, b - space-filled model.

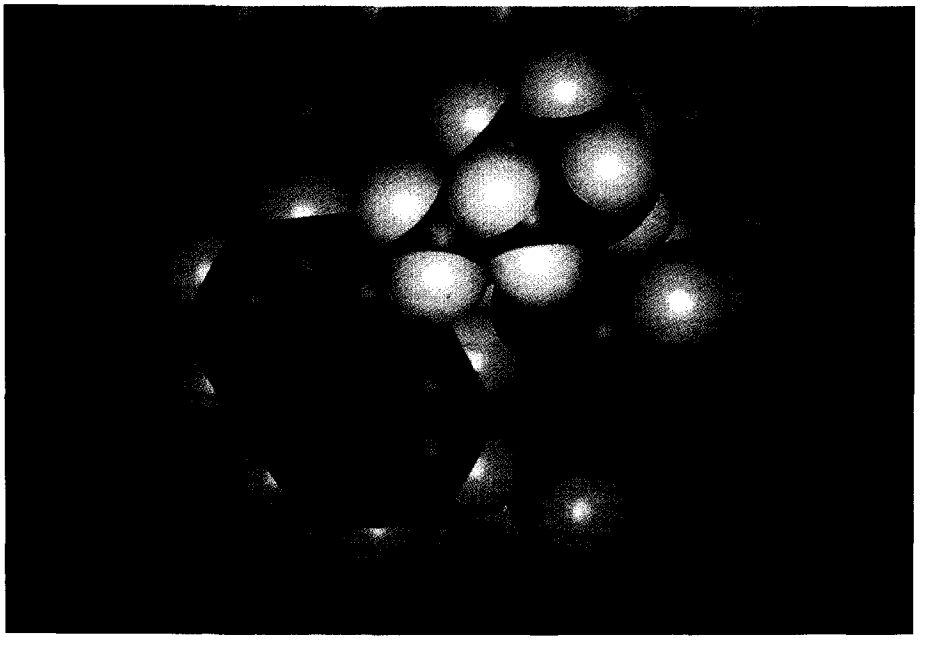


a b

Fig. 2: Calculated minimum energy for the protonated cinchonidine-methyl pyruvate adduct; a - ball and stick model, b - space-filled model.



a



b

Fig. 3: Protonated **4a**-methyl pyruvate complexes positioned onto Pt {111} surface, which yield (*R*)-methyl lactate (a) or (*S*)-methyl lactate (b) on hydrogenation.

EXPERIMENTAL

General:

All solvents were distilled before use. Unless otherwise stated, reactions were carried out under N_2 using dried glassware. Flash column chromatography: silica gel C 560, 0.035-0.070 mm, Chemische Fabrik Uetikon. TLC: silica gel 60, Merck, 0.25 mm. Spezific rotations were measured on a Perkin Elmer 241 polarimeter at room temperature, estimated error ±5%. NMR ($CDCl_3$): d in ppm *vs.* TMS, J in Hz; ^1H: 300 MHz, ^{13}C: 75 MHz, assignments based on APT spectra. IR ($CHCl_3$): selected bands in cm^{-1}. MS: selected peaks; *m/z* (%); matrix for FAB-MS: 3-nitrobenzyl alcohol.

Synthesis of Diols 2:

General procedure:[10] *(R)-(1-Naphthyl)-1,2-ethanediol* (**2a**). A mixture of 19.6 g (60 mmol) of $K_3[Fe(CN)_6]$, 82.0 g (60 mmol) of K_2CO_3, 0.154 g (0.2 mmol) of $(DHQD)_2$-PHAL and 0.0148 g (0.04 mmol) of $K_2OsO_2(OH)_4$ in 100 ml of *tert*-butyl alcohol and 100 ml of water was cooled to 0 °C. 1-Vinyl-naphthalene (3.08 g, 20 mmol) was added at once, and the heterogeneous slurry was stirred at 0 °C for 5 h. Solid sodium sulfite (30 g) was added and the mixture was allowed to warm up to room temperature and stirred for 1 h. Extraction with ethyl acetate followed by flash column chromatography with EtOAc/hexane (2:1) afforded 3.2 g (85%) of **2a** as a white solid. M.p. = 78-79 °C. Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.58; H, 6.42. Found: C, 76.80; H, 6.25. $[\alpha]_D$ = -93 (c = 1.19, $CHCl_3$, 98.5 % ee (HPLC)). > 99.5% ee was obtained *via* recrystallization twice from ether/hexane. ^1H NMR ($CDCl_3$): 8.07-8.04 (m, 1H), 7.90-7.86 (m, 1H), 7.80 (d, 1H, J = 8.2), 7.70 (d, 1H, J = 7.2), 7.55-7.46 (m, 3H), 5.64 (dd, 1H, J = 8.1, 3.2), 4.00 (dd, 1H, J = 11.4, 3.2), 3.79 (dd, 1H, J = 11.4, 8.1), 2.68 (br s, 1H, OH), 2.22 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$): 136.0 (C), 133.7 (C), 130.4 (C), 129.0 (CH), 128.4 (CH), 126.3 (CH), 125.7 (CH), 125.4 (CH), 123.5 (CH), 122.6 (CH), 71.7 (CH), 67.5 (CH_2). IR: 3687m, 3608m, 3384m, 1652s, 1261s, 1019s. MS (EI): 188 (M^+, 17), 157 (100), 129 (84), 128 (40), 127 (24). TLC (EtOAc/hexane 2:1): R_f = 0.31. HPLC: t_R = 51.2 min (*R*), 57.4 min (*S*) (Chiralcel OJ, hexane/*i*-PrOH 90/10, 0.5 mL/min, 254 nm).

Synthesis of Tosylates 3:

General procedure: (R)-2-Hydroxy-2-(1-naphthyl)ethyl tosylate (**3a**). A mixture of 1g (5.31 mmol) of diol **2a** and 805 mg (7.96 mmol) of NEt_3 in 25 ml CH_2Cl_2 was cooled to 0 °C. Tosyl chloride (1.04 g, 5.45 mmol) was added and the reaction mixture was then stirred at 5 °C for 72 h. After removal of the solvent *in vacuo*, the resulting paste was dissolved in ethyl acetate. The organic phase was washed with 1N aqueous HCl, saturated aqueous $NaHCO_3$, and saturated NaCl solution. Drying over $MgSO_4$, removal of the solvent *in vacuo* followed by flash chromatography with EtOAc/hexane (1:2) afforded the product, which was recrystallized from ether/hexane to give 1.27 g (70%) of crystalline solid. M.p. = 82-85 °C. Anal. Calcd for $C_{19}H_{18}O_4S$: C, 66.64; H, 5.29. Found: C, 66.70; H, 5.30. $[\alpha]_D$ = -130 (c = 1.07, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.87-7.66 (m, 4H), 7.49-7.40 (m, 2H), 7.25 (d, 1H, J = 9.6), 5.75 (dd, 1H, J = 8.7, 2.8), 4.36 (dd, 1H, J = 10.7, 2.8), 4.12 (dd, 1H, J = 10.7, 8.7), 3.96 (br s, 1H, OH), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$): 144.8 (C), 133.7 (C), 133.4 (C),

132.3 (C), 129.9 (C), 129.7 (CH), 128.8 (CH), 128.7 (CH), 127.7 (CH), 126.4 (CH), 125.5 (CH), 125.3 (CH), 123.9 (CH), 122.1 (CH), 73.9 (CH_2), 68.9 (CH), 21.5 (CH_3). IR: 3605m, 3608m, 1598s, 1513m, 1364s, 1176s, 1097s, 967s. MS (EI) : 342 (M^+, 42), 325 (64), 157 (100), 155 (36), 153 (70), 129 (20), 91 (22). TLC (EtOAc/hexane 1:2): R_f = 0.31.

Synthesis of Amino Alcohols 4:

General procedure: (R)-N-[2-Hydroxy-2-(1-naphthyl)ethyl]pyrrolidine (**4a**). A mixture of 342 mg (1 mmol) of tosylate **3a** and 1 ml of pyrrolidine was stirred at 40 °C for 14 h. After cooling to room temperature, the excess amine was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed twice with saturated K_2CO_3 and once with saturated NaCl solution. Drying over K_2CO_3, removal of the solvent *in vacuo* followed by flash chromatography with methanol/CH_2Cl_2/NEt_3 (10:30:1) afforded the product, which was recrystallized from ether/hexane: 150 mg of white crystalline solid (70%). M.p. = 78-79 °C. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.93; N, 5.68. Found: C, 79.92; H, 7.71; N, 5.68. $[\alpha]_D$ = -116 (c = 1.31, $CHCl_3$, > 99.5% ee (HPLC analysis of the corresponding acetate derivate)). ^1H NMR ($CDCl_3$): 8.05 (m, 1H), 7.87 (m, 1H), 7.77 (m, 2H), 7.48 (m, 3H), 5.55 (dd, 1H, J = 10.2, 3.0), 5.0-3.0 (br s, 1H, OH), 2.82 (m, 4H), 2.62 (m, 2H), 1.86 (m, 4H). ^{13}C NMR ($CDCl_3$): 138.0 (C), 133.6 (C), 130.4 (C), 128.8 (CH), 127.6 (CH), 125.7 (CH), 125.6 (CH), 125.2 (CH), 122.9 (CH), 122.8 (CH), 67.6 (CH), 63.2 (CH_2), 53.9 (CH_2), 23.6 (CH_2). IR: 3500-3200m(br), 1589m, 1512m, 1261s, 1091s, 1012s. MS (FAB): 242 ([M+H]$^+$, 100), 84 (64). TLC (methanol): R_f = 0.34. HPLC (acetate derivative): t_R = 16.3 min (*S*), 21.4 min (*R*) (Chiralcel OD, hexane/*i*-PrOH 95/5, 0.5 mL/min, 254 nm).

(R)-N-[2-Hydroxy-2-(4-quinolyl)ethyl]pyrrolidine (**4b**). The product was recrystallized from ether/hexane and sublimed at 100 °C, 0.1 mmHg (40% overall yield based on 4-vinylquinoline, white needles). M.p. = 89-90 °C. Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.33; H, 7.43; N, 10.60. $[\alpha]_D$ = -131 (c = 0.50, $CHCl_3$, > 99.9% ee (HPLC analysis of the corresponding benzoate derivate, minor enantiomer could not be detected)). ^1H NMR ($CDCl_3$): 8.93 (d, 1H, J = 4.4), 8.15 (d, 1H, J = 8.5), 7.99 (d, 1H, J = 8.5), 7.74-7.69 (m, 2H), 7.58-7.53 (m, 1H), 5.52 (dd, 1H, J = 8.6, 4.7), 4.0 (br s, 1H, OH), 2.90-2.81 (m, 4H), 2.69-2.60 (m, 2H), 1.93-1.80 (m, 4H). ^{13}C NMR ($CDCl_3$): 150.6 (CH), 148.2 (C), 148.0 (C), 130.5 (CH), 128.9 (CH), 126.4 (CH), 125.7 (C), 122.7 (CH), 117.6 (CH), 66.8 (CH), 62.7 (CH_2), 54.0 (CH_2), 23.8 (CH_2). IR: 3403m(br), 1711m, 1594m, 1572w, 1509m, 1352w, 1099s, 1015s. MS (FAB): 243 ([M+H]$^+$, 100), 156 (31), 84 (61), 72 (25). TLC (ethanol/NEt_3 50:1): R_f = 0.35. HPLC (benzoate derivative): t_R = 19.0 min (*R*), 25.3 min (*S*) (Chiralcel OD, hexane/*i*-PrOH 90/10, 0.5 mL/min, 254 nm).

(S)-N-[2-Hydroxy-2-phenylethyl]pyrrolidine (**4c**). The product was recrystallized from ether/hexane (70% overall yield based on (*S*)-(+)-1-phenyl-1,2-ethanediol, white crystalline solid). M.p. = 67-68 °C. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.39; H, 8.85; N, 7.31. $[\alpha]_D$ = +58 (c = 0.89, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.42-7.25 (m, 5H), 4.71 (dd, 1H, J = 10.7, 3.3), 3.7 (br s, 1H, OH), 2.83-2.74 (m, 3H), 2.59-2.47 (m, 3H), 1.87-1.80 (m, 4H). ^{13}C NMR ($CDCl_3$): 142.5 (C), 128.3 (CH), 127.4 (CH), 125.9 (CH), 70.7 (CH), 64.1 (CH_2), 53.8 (CH_2), 23.7 (CH_2). IR: 3414m(br), 1606w, 1496m, 1454m, 1407m, 1351m, 1090s, 1061s, 1028, 898s. MS (FAB): 192 ([M+H]$^+$, 100), 84 (50), 72 (17). TLC (acetone/NEt_3 100:1): R_f = 0.29.

(R)-N-[2-Hydroxy-2-(4-pyridyl)ethyl]pyrrolidine (**4d**). The product was recrystallized from ether/hexane (30% overall yield based on 4-vinylpyridine, white crystalline solid). M.p. = 80-81 °C. Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.73; H, 8.28; N, 14.49. $[\alpha]_D$ = -63 (c = 0.96, $CHCl_3$). ^1H NMR ($CDCl_3$): 8.56 (d, 2H, J = 5.6), 7.31 (d, 2H, J = 5.6), 4.68 (dd, 1H, J = 10.4, 3.7), 4.1 (br s, 1H, OH), 2.76-2.66 (m, 3H), 2.58-2.50 (m, 3H), 1.83-1.79 (m, 4H). ^{13}C NMR ($CDCl_3$): 151.6 (C), 149.7 (CH), 120.7 (CH), 69.3 (CH), 63.3 (CH_2), 53.8 (CH_2), 23.7 (CH_2). IR: 3398m(br), 1604s, 1414s, 1352m, 1310m, 1098m, 1067m, 903m. MS (FAB): 193 ($[M+H]^+$, 100), 106 (21), 84 (39), 72 (22). TLC (ethanol/NEt_3 100:1): R_f = 0.12.

(S)-N-[2-Hydroxy-2-(2-naphthyl)ethyl]pyrrolidine (**4e**). After sublimation at 100 °C (0.1 mmHg) a white solid was obtained (30% overall yield, based on 2-vinyl-naphthalene). M.p. = 118.5-119.5 °C. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.93; N, 5.68. Found: C, 79.40; H, 8.02; N, 5.75. $[\alpha]_D$ = +40 (c =1.02, EtOH). ^1H NMR ($CDCl_3$): 7.88-7.82 (m, 4H), 7.52-7.27 (m, 3H), 4.88 (dd, 1H, J = 10.6, 3.3), 4.1 (br s, 1H, OH), 2.90-2.77 (m, 3H), 2.61-2.55 (m, 3H), 1.88-1.59 (m, 4H). ^{13}C NMR ($CDCl_3$): 140.5 (C), 133.9 (C), 133.6 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 126.5 (CH), 126.2 (CH), 125.1 (CH), 124.6 (CH), 71.4 (CH), 64.6 (CH_2), 54.5 (CH_2), 24.3(CH_2). IR (KBr): 3422s, 1597m, 1358m, 1121s, 1073s. MS (FAB): 242 ($[M+H]^+$, 100), 224 (25), 84 (51), 72 (37). TLC (methanol/acetone 1:1): R_f = 0.15.

(R)-[2-Hydroxy-2-(1-naphthyl)ethyl]dimethylamine (**4f**). After sublimation at 80 °C (0.1 mmHg) a white solid was obtained (40% overall yield, based on 1-vinyl-naphthalene). M.p. = 64-66.5 °C. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.20; H, 7.97; N, 6.46. $[a]_D$ = -154 (c = 0.40, EtOH). ^1H NMR ($CDCl_3$): 8.01 (dd, 1H, J = 8.3, 2.2), 7.87 (dd, 1H, J = 7.7, 1.4), 7.80-7.78 (m, 2H), 7.52-7.46 (m, 3H), 5.54 (dd, 1H, J = 10.2, 3.3), 2.71-2.55 (m, 3H), 2.44 (s, 6H). ^{13}C NMR ($CDCl_3$): 137.7 (C), 133.7 (C), 130.5 (C), 128.9 (CH), 127.6 (CH), 125.8 (CH), 125.7 (CH), 125.3 (CH), 123.0 (CH), 122.7 (CH), 66.5 (CH), 66.4 (CH_2), 45.4 (CH_3). IR (KBr): 3367s, 1638m, 1596m, 1458s, 1320m, 1086s, 1029s, 874m. MS (CI, NH_3): 216 ($[M+H]^+$, 100), 58 (35). TLC (methanol/acetone 1:1): R_f = 0.31.

(R)-[2-Hydroxy-2-(1-naphthyl)ethyl]diisobutylamine (**4g**). Colorless oil, 35% overall yield, based on 1-vinyl-naphthalene. Anal. Calcd for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.42; H, 9.81; N, 4.72. $[\alpha]_D$ = -202 (c = 0.13, $CHCl_3$). ^1H NMR ($CDCl_3$): 8.07 (m, 1H), 7.92-7.79 (m, 3H), 7.57-7.45 (m, 3H), 5.54 (dd, 1H, J = 10.4, 3.3), 4.37 (s. 1H, OH), 2.81 (dd, 1H, J = 12.9, 3.3), 2.65 (dd, 1H, J = 12.9, 10.4), 2.44 (dd, 2H, J = 12.4, 9.6), 2.32 (dd, 2H, J = 12.4, 4.4), 1.93-1.87 (m, 2H), 1.10 (d, 6H, J = 6.3), 0.99 (d, 6H, J = 6.6). ^{13}C NMR ($CDCl_3$): 137.9 (C), 133.7 (C), 130.6 (C), 128.9 (CH), 127.6 (CH), 125.7 (CH), 125.6 (CH), 125.2 (CH), 123.0 (CH), 122.8 (CH), 66.5 (CH), 63.9 (CH_2), 63.3 (CH_2), 26.3 (CH), 21.1 (CH_3), 20.9 (CH_3). IR: 3419m(br), 1689m, 1598m, 1512m, 1468s, 1392s, 1367s, 1089s, 868m. TLC (EtOAc/hexane 1:9): R_f = 0.43.

(R)-N-[2-Hydroxy-2-(1-naphthyl)ethyl]morpholine (**4h**). The product was recrystallized from EtOAc/hexane (45% overall yield based on 1-vinyl-naphthalene, white crystalline solid). M.p. = 73-74 °C. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.72; H, 7.51; N, 5.50. $[\alpha]_D$ = -121 (c = 0.36, $CHCl_3$). ^1H NMR ($CDCl_3$): 8.01-7.98 (m, 1H), 7.89-7.86 (m, 1H), 7.78 (d, 2H, J = 7.7), 7.53-7.47 (m, 3H), 5.60 (dd,

1H, J = 10.6, 2.8), 3.83-3.77 (m. 4H), 2.87-2.81 (m, 3H), 2.64-2.50 (m, 3H). ^{13}C NMR ($CDCl_3$): 137.4 (C), 133.7 (C), 130.5 (C), 129.0 (CH), 127.9 (CH), 126.0 (CH), 125.7 (CH), 125.5 (CH), 123.1 (CH), 122.6 (CH), 67.1 (CH), 65.7 (CH_2), 65.6 (CH_2), 53.6 (CH_2). IR: 3438m(br), 1598m, 1513m, 1456s, 1298m, 1137s, 1117s, 1007m, 873s. TLC (EtOAc/hexane 2:1): R_f = 0.22.

(R)-[2-Hydroxy-2-(1-naphthyl)ethyl]methylamine (**4i**). Light yellow solid, 40% overall yield, based on 1-vinyl-naphthalene. M.p. = 82-83 °C. $[\alpha]_D$ = -105 (c = 0.25, $CHCl_3$). ^1H NMR ($CDCl_3$): 8.04-8.00 (m, 1H), 7.86-7.82 (m, 1H), 7.76-7.69 (m, 2H), 7.48-7.41 (m, 3H), 5.55 (dd, 1H, J = 8.7, 3.3), 3.13 (br.s, 2H, NH and OH), 2.99 (dd, 1H, J = 12.1, 3.3), 2.83 (dd, 1H, J = 12.1, 8.7), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$): 138.0 (C), 133.7 (C), 130.4 (C), 128.9 (CH), 127.9 (CH), 126.0 (CH), 125.5 (CH), 125.4 (CH), 123.0 (CH), 122.8 (CH), 68.4 (CH), 58.1 (CH_2), 36.1 (CH_3). IR (KBr): 3440m(br), 3323s, 1594m, 1508m, 1458s, 1117s, 1080s. MS (CI, NH_3): 202 ($[M+H]^+$, 100), 184 (25), 44 (30). TLC (methanol/NEt_3 100:1): R_f = 0.25.

(2R,1'S)-[2-Hydroxy-2-(1-naphthyl)ethyl]-[1'-phenylethyl]amine (**4j**). Colorless oil, 35% overall yield, based on 1-vinyl-naphthalene. Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.77; H, 7.35; N, 4.86. $[\alpha]_D$ = -177 (c = 0.13, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.89-7.82 (m, 2H), 7.74 (d, 1H, J = 8.2), 7.65 (d, 1H, J = 7.2), 7.47-7.39 (m, 3H), 7.37-7.22 (m, 5H), 5.51 (dd, 1H, J = 9.0, 3.2), 3.92 (q, 1H, J = 6.6), 3.06 (dd, 1H, J = 12.5, 3.2), 2.67 (dd, 1H, J = 12.5, 9.0), 1.43 (d, 3H, J = 6.6). ^{13}C NMR ($CDCl_3$): 145.0 (C), 138.0 (C), 133.6 (C), 130.3 (C), 128.8 (CH), 128.6 (CH), 127.8 (CH), 127.1 (CH), 126.5 (CH), 125.8 (CH), 125.5 (CH), 125.3 (CH), 122.9 (CH), 122.8 (CH), 68.7 (CH), 57.4 (CH), 53.6 (CH_2), 24.4 (CH_3). IR: 3667w, 3607m, 3360s(br), 1679m, 1598s, 1512s, 1494s, 1451s, 1117s, 1078s, 898m, 862m. TLC (acetone/hexane 1:1): R_f = 0.36.

(2R,1'R)-[2-Hydroxy-2-(1-naphthyl)ethyl]-[1'-phenylethyl]amine (**4k**). White solid, 45% overall yield, based on 1-vinyl-naphthalene. M.p. = 130-131 °C. Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.98; H, 7.47; N, 4.81. $[\alpha]_D$ = -31 (c = 0.32, $CHCl_3$). ^1H NMR ($CDCl_3$): 7.86-7.68 (m, 4H), 7.50-7.42 (m, 3H), 7.35-7.33 (m, 4H), 7.28-7.25 (m, 1H), 5.32 (dd, 1H, J = 8.2, 3.5), 3.79 (q, 1H, J = 6.6), 3.01 (dd, 1H, J = 3.5, 12.3), 2.81 (dd, 1H, J = 12.3, 8.2), 1.39 (d, 3H, J = 6.6). ^{13}C NMR ($CDCl_3$): 145.4 (C), 138.2 (C), 133.7 (C), 130.4 (C), 128.9 (CH), 128.6 (CH), 127.8 (CH), 127.2 (CH), 126.7 (CH), 125.9 (CH), 125.5 (CH), 125.4 (CH), 122.9 (CH), 122.8 (CH), 69.4 (CH), 58.7 (CH), 54.3 (CH_2), 24.4 (CH_3). IR: 3688w, 3608m, 3446m(br), 1598s, 1512s, 1494s, 1552s, 1120s, 895m. TLC (acetone/hexane 1:1): R_f = 0.33.

Synthesis of Oxazolidine 5:

(R)--5-(1-Naphthyl)-N-methyloxazolidine (**5**). A mixture of 100 mg (0.5 mmol) amino alcohol **4i** and 30 mg of $(CH_2O)_3$ was refluxed in 10 ml of toluene with a Dean-Stark trap during 14 h. Removal of the solvent and excess of $(CH_2O)_3$ *in vacuo* afforded the product as white solid, which was further purified by sublimation at 55 °C, 0.1 mmHg; 74.5 mg, 70% yield. M.p. = 62.5-64.5 °C. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.69; H, 7.11; N, 6.47. $[\alpha]_D$ = -138 (c = 0.25, EtOH). ^1H NMR ($CDCl_3$): 7.90-7.84 (m, 2H), 7.78-7.73 (m, 2H), 7.52-7.46 (m, 3H), 5.76 (dd, 1H, J = 7.2, 7.1), 4.64 (d, 1H, J = 5.0), 4.60 (d, 1H, J = 5.0), 3.64 (dd, 1H, J = 11.2, 7.1), 2.86 (dd, 1H, J = 11.2, 7.2), 2.56 (s, 3H). ^{13}C NMR ($CDCl_3$): 138.1 (C),

133.7 (C), 130.2 (C), 128.9 (CH), 127.5 (CH), 126.0 (CH), 125.7 (CH), 125.5 (CH), 122.9 (CH), 121.5 (CH), 89.0 (CH_2), 74.1 (CH), 62.1 (CH_2), 41.9 (CH_3). IR (KBr): 1594m, 1457m, 1329m, 1062s, 1019s, 981s, 897s. MS (CI, NH_3): 214 ($[M+H]^+$, 100), 57 (33).

Hydrogenation of ethyl pyruvate:

A 5% Pt/Al_2O_3 catalyst (Engelhard 4759, 50 mg for hydrogenations performed at 1 bar, 10 mg for hydrogenations performed at 25 and 75 bar) was reduced in flowing argon for 45 min and then hydrogen for 120 min, all at 673 K before being cooled to room temperature in flowing argon. Catalysts to be used at 1 bar were transferred under argon into 2 ml of acetic acid containing 33.4 μmol of modifier into a glass tube. Catalysts to be used at higher pressures were first exposed to air before being transferred in 2 ml of acetic acid containing 6.8 μmol of modifier in a 50 ml stainless steel autoclave. In each case 10.2 mmol of freshly distilled ethyl pyruvate (Aldrich) was added to the mixture and the reaction vessel charged to the desired pressure. Reaction proceeded at 293 K until no further pressure drop was observed. Conversion and enantioselectivity were determined by glc analysis (permethylated β-cyclodextrin, Chrompack).

Molecular Modelling:

The BIOSYM programs, InsightII and Discover 2.9/3.1 were used in the molecular modelling study. Minimum energy conformations of the modifiers were determined by a combined approach of high temperature molecular dynamic simulations at 700 K for 100 ps with molecular mechanics minimisation performed at 1 ps intervals using the CVFF forcefield and the VAO9A algorithm, or by molecular mechanics minimisation alone using the default values as suplied by the software. Minimum energy calculations were performed to calculate the complex of **4a** and methyl pyruvate. In the other cases the molecules were simply positioned, relative to the Pt atoms, adsorbing the aromatic rings and carbonyl groups over the Pt atoms. Calculation involving the Pt surface was not possible.

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