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(54) Title: PROCESS FOR OBTAINING ENANTIOMERS OF THIENYLAZOLYLALCOXYETHANAMINES

(57) Abstract: A process is described for the preparation of a precursor alcohol of (±)-2-[thienyl(1-methyl-1H-pyrazol-5-yl)methoxy]-N,N-dimethyletanamine and in general for thyenylazolylalcoxyethanamines and their enantiomers. It comprises the asymmetric reduction of a prochiral ketone in the presence of a chiral ruthenium (II) catalyst system comprising at least a bidentate phosphorous-containing ligand and a diamine ligand to render chiral alcohols. The chiral alcohols are further O-alkylated to render the corresponding pharmaceutically active ethanamines.

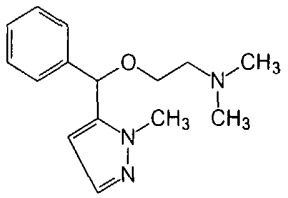
PROCESS FOR OBTAINING ENANTIOMERS OF THIENYLAZOLYLALCOXYETHANAMINES

FIELD OF THE INVENTION

The present invention relates to a new process for the preparation of enantiomerically enriched carbinols substituted simultaneously with pyrazolyl and thienyl heterocycles. The process comprises the enantioselective asymmetric hydrogenation of ketones using chiral catalytic systems to render nonracemic chiral alcohols. More particularly, it relates to a new process for the preparation of the pure enantiomers of intermediate alcohols that are useful intermediates for the preparation of pharmaceutically active thyenylazolylalcoxyethanamines.

BACKGROUND OF THE INVENTION

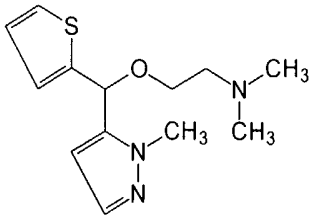
The compound (±)-2-[phenyl(1-methyl-1*H*-pyrazol-5-yl)methoxy]-*N,N*-dimethylethanamine, also referred to as (±)-5-[α-(2-dimethylaminoethoxy)benzyl]-1-methyl-1*H*-pyrazole, or Cizolirtine of formula



was described in the European patent EP 289 380. This compound is a potent analgesic which is currently in phase II clinical trials. Optical resolution by fractional crystallization with optically active acids has been applied to the Cizolirtine racemate (WO 99/02500).

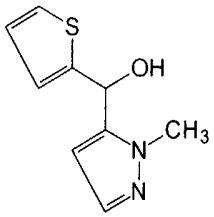
A further family of active compounds wherein a thiophene ring is present instead of the phenyl ring has been described in WO 99/52525. Among them, the compound (±)-2-[thienyl(1-methyl-1*H*-pyrazol-5-yl)methoxy]-*N,N*-dimethylethanamine of formula (I)

CONFIRMATION COPY



(I)

is currently in clinical trials for the treatment of depression. It can be prepared by O-alkylation of the compound of formula II:



(II)

The carbinols such as the one of formula II are key intermediates to reach the compounds described in WO 99/52525. The pure enantiomers of (+)-I and (-)-I may be prepared by separately O-alkylating the enantiomerically pure intermediates (+)-II and (-)-II. Thus, a synthetic process to the enantiomerically pure/enriched intermediates (+)-II and (-)-II is needed.

The enantioselective reduction of prochiral ketones has been proposed in organic synthesis to obtain secondary alcohols with high enantiomeric purity. Accordingly, a number of strategies for the asymmetric reduction of prochiral ketones to single enantiomer alcohols have been developed [R. Noyori, T. Ohkuma, *Angew. Chem. Int. Ed.*, 2001, 40, 40-73].

A strategy for the enantioselective reduction of aromatic and heteroaromatic prochiral ketones with high ee values comprises the use of an optically active diphosphane/Ru/diamine/inorganic base catalyst system. Examples of asymmetric reduction of heteroaromatic ketones are disclosed in WO 2004/011452 and in P. Cao, X. Zhang, *J. Org. Chem.* 1999, *64*, 2127. Enantioselective hydrogenation of ketonic structures to nonracemic secondary alcohols has been achieved with also a wide range of chiral ruthenium catalyst systems which can be prepared by different combinations of Ru (II) chiral phosphanes and diamine ligands. The extent of the enantioselectivity

obtained with the different ketones depends largely on the nature of the substituents of the prochiral ketone as shown by the state of the art [see, for instance, Table 2, on p. 53: R. Noyori, T. Ohkuma, Angew. Chem. Int. Ed. 2001, 40, 40-73]. It is also known that heteroaromatic ketones can be enantioselectively hydrogenated to nonracemic secondary alcohols with these chiral ruthenium catalysts systems [C. Chen, R. A. Reamer, J. R. Chilenski, C. J. McWilliams, *Org. Lett.* **2003** *5*, 5039].

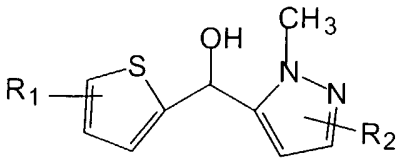
However it has been found that one specific catalyst or a class of catalysts cannot be used equally well in all hydrogenations. Thus, to attain satisfactory ee values by the enantioselective hydrogenation of prochiral ketones, each hydrogenation problem has to be investigated separately with regard to the substrate, the catalyst and the reaction conditions for finding the optimal conditions to obtain the best results.

The object of the present invention was to provide a process for the enantioselective hydrogenation of a thienyl pyrazoyl ketone. This process should operate particularly well on industrial scale and be satisfactory as regards yield, conversion and enantiomer excess. In particular the process should be suitable for providing in an advantageous manner specific enantiomer-enriched alcohols as intermediates for the preparation of (+)- and (-)-thienylazolylalcoxyethanamines.

SUMMARY OF THE INVENTION

Surprisingly, the inventors have achieved the enantioselective hydrogenation with a chiral ruthenium (II) catalyst system of a prochiral ketone with a thienyl and a methyl-pyrazol substituent comprising two nitrogen atoms, with high ee value and very high conversion. Investigations carried out by the inventors have shown in a no foreseeable manner, that the prochiral ketone with a thienyl and a methyl-pyrazol substituent provides the catalytical enantioselective hydrogenation of said ketone with high enantioselectivity and excellent conversion. This could not have been predicted from the nature of the substrate. We have therefore applied this process to the synthesis of the enantiomerically pure intermediates (+)-II and (-)-II and to a process to obtain 2-[thienyl(1-methyl-1*H*-pyrazol-5-yl)methoxy]-*N,N*-dimethylethanamine and in general thienylazolylalcoxyethanamines and their enantiomers. This process should operate particularly well on an industrial scale and be satisfactory with regard to enantiomer excess, amount and availability of catalyst and in general raw material costs.

Accordingly, the present invention is directed to a process for the preparation of an enantiomerically enriched compound of formula (II):

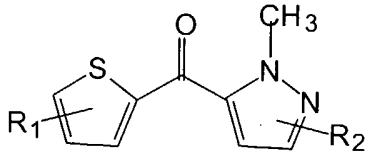


(II)

wherein:

R_1 and R_2 are independently selected from hydrogen, halogen, lower alkyl or aryl;

which comprises the asymmetric hydrogenation of a prochiral ketone of formula (III)



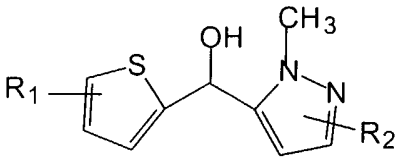
(III)

in the presence of a base and a chiral ruthenium (II) catalyst system comprising at least a bidentate phosphorous-containing ligand and a diamine ligand.

In a preferred embodiment either of R_1 or R_2 is H, preferably both are H.

Said process allows the preparation of the known intermediates of formula II, which can be optionally transformed in enantiomerically pure pharmaceutically active compounds.

According to a further aspect, the present invention is directed to a process for the preparation of an enantiomerically enriched compound of formula (II):

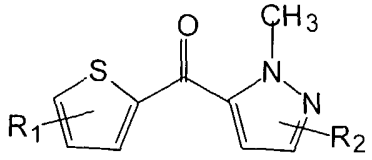


(II)

wherein:

R_1 and R_2 are independently selected from hydrogen, halogen, lower alkyl or aryl;

which comprises the asymmetric hydrogenation of a prochiral ketone of formula (III)



(III)

in the presence of a base and a chiral ruthenium (II) catalyst system comprising at least a bidentate phosphorous-containing ligand selected from TolBINAP and BINAP and a diamine ligand selected from DPEN and DAIPEN.

DETAILED DESCRIPTION OF THE INVENTION

The process of the invention gives the desired product of formula II with high conversion and enantiomeric excess. This process has the further advantage that the starting materials are not expensive and that it works under low or normal pressures. Similar hydrogenations are known, as mentioned above, but it is the first time they are applied to a thienyl pyrazol ketone substrate. Although problems due to the coordination of the pyrazol could have been expected, we have found on the contrary that the reaction works remarkably well providing a simple route to the alcohols of formula (II) with high conversion and enantiomeric excess. It allows the compounds of the above formula (II) to be synthesised directly from the compounds of formula (III), without any further intermediate steps or laborious separation of the isomeric forms.

The product of formula II is especially useful in the preparation of the enantiomers of (±)-2-[thienyl(1-methyl-1*H*-pyrazol-5-yl)methoxy]-*N,N*-dimethyl-ethanamine, among others. It will be readily apparent to the person skilled in the art that the process is also applicable to the hydrogenation of other ketones comprising a thienyl substituent and having a different nitrogen-containing heterocycle instead of the methyl pyrazole ring, such as methyl pyrrole, methyl imidazole and methyl triazole. Different compounds can be obtained depending on the substituents present on the thienyl or N-containing heterocyclic rings.

We will discuss below the different reagents and conditions for the process of the invention.

The chiral ruthenium (II) catalyst system used in the process of the present invention is known to the person skilled in the art and is composed of Ruthenium (II) complexes with two different ligands, a bidentate phosphorous-containing ligand and a diamine, in the presence of a base. Said catalyst system components can be provided to the reaction mixture individually to form the reactive catalyst system *in situ* or they can be provided as preformed complexes.

The bidentate phosphorous-containing ligand is in general of the biphosphines or biphosphites types, more preferably it is of the biphosphine type. Illustrative examples of nonracemic chiral diphosphines are 2,2'-bis(diphenyl-phosphino)-1,1'-binaphtyl (BINAP), TolBINAP and XylBINAP [R. Noyori, T. Ohkuma, Angew. Chem. Int. Ed., 2001, 40, 40-73], 2,2'-bis(diphenylphosphino)-1,1'-dicyclopentane (BICP) [P. Cao, X. Zhang, *J. Org. Chem.* **1999** *64*, 2127-2129], 2,2',6,6'-tetramethoxy-4,4'-bis(diphenylphosphino)-bis-3,3'-bipyridine (P-Phos), Tol-P-Phos and Xyl-P-Phos [J. Wu, H. Chen, W. Kwok, R. Guo,Z. Zhou, C. Yeung, A. S. C. Chan, *J. Org. Chem.* **2002**, *63*, 7908-7910], 4,12-bis(diphenylphosphino)[2.2]paracyclophane (PhanePhos) and Xyl-PhanePhos [M. J. Burk, W. Hems, D. Herzberg, C. Malan, A. Zanotti-Gerosa, *Org. Lett.* **2000**, *2*, 4173-4176] and equivalents thereto that are recognized by those skilled in the art.

In one preferred embodiment the diphosphine ligand comprises a binaphthyl group. They are more preferably selected from the group consisting of the enantiomers of 2,2'-bis(diphenyl-phosphino)-1,1'-binaphtyl (BINAP), TolBINAP and XylBINAP [see R. Noyori, T. Ohkuma, Angew. Chem. Int. Ed., 2001, 40, 40-73].

Suitable diamines are 1,2-diamine species that exhibit a sufficient activity or selectivity in the catalyst under consideration. They can be chiral or non-chiral. Illustrative examples are any stereoisomers of 1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine (DAIPEN), 1,2-diphenylethylendiamine (DPEN), 1,2-diaminocyclohexane (DACH) or achiral diamines such as ethylenediamine. Achiral amines are further discussed in US 6,743,921 which is incorporated herein by reference in its entirety.

The use of enantiomeriacally enriched diamines such as DAIPEN and DPEN has proved particularly advantageous, DPEN regards costs and DAIPEN regards higher activity and selectivity.

The bidentate phosphorous-containing ligand together with the diamine and the ruthenium (II) form a complex referred to hereinafter as the ruthenium (II) component of the catalyst system. Examples of preformed complexes of the ruthenium with the diphosphine ligand and the diamine include complexes represented by the formula RuX_2LA wherein X represents a halogen atom or pseudo-halide group, preferably chloride or bromide, L represents the diphosphine ligand and A is the diamine. Suitable examples are $RuCl_2$ [(S)-BINAP][(R,R)-DPEN], $RuCl_2$ [(S)-BINAP][(S,S)-DPEN], $RuCl_2$ [(R)-BINAP][(R,R)-DPEN], $RuCl_2$ [(R)-BINAP][(S,S)-DPEN], $RuCl_2$ [(R)-BINAP][(R)-DAIPEN], $RuCl_2$ [(S)-BINAP][(S)-DAIPEN].

Specially good conditions have been achieved with the use of $RuCl_2$ [TolBINAP][DPEN] (see Table 2).

Said component is present in catalytic amounts, meaning less than stoichiometric relative to the ketone reactants and as low as possible while ensuring the optimum possible conversion rate. The minimum amount of the ruthenium (II) component of the catalyst system may depend on the activity of the specific catalyst system composition, the reaction temperature, the concentration of the reactants and catalyst system components in the solution, and the maximum time allowed for completion of the reaction. In a typical embodiment the molar ratio of the ruthenium (II) component of the catalyst to the ketone reactant (s/c) is in the range from about 50 to 20,000, preferably from about 200 to about 20,000, more preferably from about 10,000 to about 20,000.

Suitable bases include organic bases and inorganic bases which should not have a negative influence on, for example, the enantiomer purity of the products that are formed. Preferably, the base is selected from the group consisting of a hydroxide, C_1-C_5-alkoxide, bicarbonate, carbonate, di- and tribasic phosphate, borate, fluoride, amine optionally substituted with C_1-C_4-alkyl or aryl, silane optionally substituted with C_1-C_3-alkyl.

In this connection alkali metal alcoholates are advantageous, such as for example *t*-BuOK, as well as inorganic bases such as for example KOH or K_2CO_3. Also organic nitrogen bases such as NEt_3 and salts as for example $AgCF_3SO_3$ are used. In a more preferred embodiment *t*-BuOK is used. When the base used is *t*-BuOK it is preferably added to the reaction vessel in form of a solution of *t*-BuOK in *t*-BuOH.

It has been found that a molar excess of base referred to the ruthenium (II) component of the catalyst system is advantageous. The typical mole ratio base: ruthenium (II) component of the catalyst system is comprised between 10:1 and 1, more preferably between about 6:1 and about 4:1. It has been found that both the activity and the selectivity of the hydrogenation vary with the amount of the base. In this connection the activity of the hydrogenation increases with rising concentration of the base. However, if the concentration of base is too high there is a possibility of racemization of the end product, which is not desirable. A ratio of about 6:1 is particularly preferred.

The hydrogenation reaction is conducted in a solvent system that is capable of dissolving the catalyst system and is reaction-inert. The term solvent system is used to indicate that a single solvent or a mixture of two or more solvents can be used. The term reaction-inert is used to mean that the solvent system does not react unfavourably with the reactants, products, or the catalyst system. The solvent system need not bring about complete solution of the ketone reactant or the chiral alcohol product. The ketone reactant may be incompletely dissolved at the beginning of the reaction or the chiral alcohol product may be incompletely dissolved at the end of the reaction, or both. Representative solvents are alcohol solvents such as methanol, ethanol, n-propanol, 2-propanol, n-butanol, *sec*-butanol or *t*-butanol and their mixtures, organic solvents containing heteroatoms such as DMF and ethers like THF. Preferably the solvent system comprises an alcohol solvent, more preferably methanol, isopropanol, *t*-butanol and their mixtures. *Tert*-butanol is particularly preferred.

The hydrogenation takes place in a suitable reactor known to the person skilled in the art, such as an autoclave. It is advisable to carry out the hydrogenation under an inert gas atmosphere. Suitable media are nitrogen gas or a noble gas such as argon.

The temperature during the reaction may in principle be chosen arbitrarily by the person skilled in the art as long as a sufficient quick and selective reaction is guaranteed. However, it has to be taken into account that the temperature depends strongly on solvent and that some catalyst systems are instable above 40 °C. In typical embodiments the reaction is suitably conducted at a temperature comprised between 10-45 °C, preferably between 20-35 °C.

The hydrogenation refers to reacting the ketone with a source of hydrogen atoms under appropriate conditions so that two hydrogen atoms are added to the carbonyl

group of the ketone to produce the hydroxyl group of the chiral alcohol. Preferably the source of hydrogen atoms includes molecular hydrogen (H_2). If the hydrogenation is carried out in the presence of molecular hydrogen, the hydrogen pressure in the reaction is preferably low, typically at least about a 1.3 bar. Normally it is in the range from 0.8 to 100 bar. More typically the hydrogen pressure is in the range from 1.3 to 8 bar.

The ketone of formula (III) is known and can be prepared as described for example in WO99/52525 or any other method readily apparent to the person skilled in the art. Normally the ketone substrate (III), the catalyst system and the base (if it is a solid) are weighted and introduced in the reactor. Then the solvent is added and stirred to complete dissolution of the catalyst. Thereafter the base, if not a solid, is added. The reactor is brought to the adequate temperature and pressure to complete the reaction. Alternatively, the ketone of formula (III) is dissolved in an appropriate solvent, then the constituents of the catalyst system or the catalyst in preformed form are added, and then the hydrogenation is performed at an appropriate temperature and suitable hydrogen pressure.

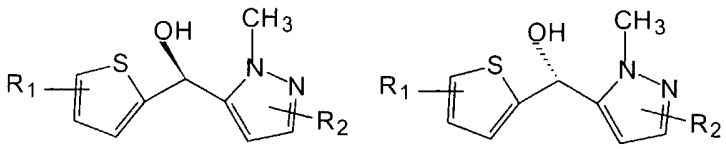
The ketone concentration ranges from about 0.025 to 0.125 mol/l, preferably from about 0.05 to 0.1 mol/l. In general the reaction is allowed to continue until complete conversion of the ketone. Times comprised between 1 to 110 hours are sufficient, although shorter times are preferred in terms of economy of the process.

The advantages associated with the invention are numerous: The process according to the invention provides a simple means of access to isomers which were previously relatively difficult to obtain, and also allows this to be done on a large industrial scale with excellent productivity. The process according to the invention makes it possible to prepare the desired product not only in high yields but also with very high enantioselectivity. No additional purification steps are needed, the products may be further processed directly just as they occur.

Conversions of 100% of the ketone are achieved by the process of the present invention. The enantiomers proportions achieved by the process of the invention are above 94 ee%. Since the constituents of the catalyst (diamine, ruthenium (II) and bidentate phosphorous containing ligand) may be used in several diasteromeric and enantiomeric forms and the complex in each case may therefore be present in so-called

matched or mismatched configurations with regard to the chiral ketone, the person skilled in the art must check which pair works most suitably regards selectivity.

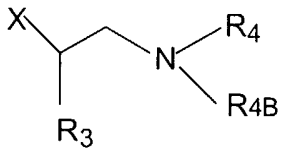
In a preferred embodiment the process is directed to the synthesis of each of the following alcohols of formula II with the highest possible enantiomeric purity:



wherein R_1 and R_2 are as defined above.

It will be readily apparent to the person skilled in the art that the process is also applicable for the hydrogenation of other thienyl ketones having a different nitrogen-containing heterocycle instead of the pyrazole ring, such as pyrrole, imidazole and triazole.

Thus, in another aspect, the invention relates to a process as defined above which further comprises the step of O-alkylation of an enantiomerically enriched compound of formula (II) to yield the desired enantiomer of a pharmaceutically active compound as described in WO 99/52525. To this end the compound of formula (II) is treated with an amine of formula



wherein

X is a suitable leaving group such as halogen, more preferably chlorine, bromine or iodine; a reactive esterified hydroxyl, for example arylsulphonyloxy such as phenylsulphonyloxy; tosyloxy; mesyloxy; C_{1-4} alkyl sulphonyloxy, for example methanesulphonyloxy; arylphosphoryloxy, for example diphenylphosphoryloxy, dibenzylphosphoryloxy or a C_{1-4} alkyl phosphoryloxy, for example dimethylphosphoryloxy, and R_3, R_4 and R_{4B} are independently selected from H and a lower alkyl.

Preferably R_3 is hydrogen.

Preferably R_4 and R_{4B} are independently selected from H and methyl.

In one embodiment both R_4 and R_{4B} are methyl.

A particularly preferred amine for the step of O-alkylation is X-CH_2-$CH_2N(Me)_2$. More preferably X is chlorine.

The O-alkylation has been described in WO 99/52525, the content of this patent application is incorporated herein in its entirety.

The alkylation is preferably carried out directly in the same reaction medium resulting from the process of the invention, without further purification of the carbinol. In general, the O-alkylation is carried out in conditions of phase transfer, using for example 2-chloro-*N,N*,-dimethylethylamine (other leaving groups instead of chloro are possible), an alkaline aqueous solution such as NaOH or KOH, in the presence of a catalyst such as a quaternary ammonium salt. Accordingly, the same solvent as the one used in the process of the invention is used, such as toluene. In these conditions we have the further advantage that the impurities like any remaining zinc salts are also eliminated through the aqueous phase.

The resulting product of formula I is enantiomerically enriched; it can be further purified using polar organic solvents. Further, a pharmaceutically acceptable salt of the obtained compound can be formed. For example, the citrate salt can be prepared by dissolving the amine of formula I in ethanol and treating the solution with citric acid monohydrate. The preparation of other salts will be readily apparent to the person skilled in the art.

The following examples will further illustrate the invention and they should not be interpreted as limiting the scope of the invention.

EXAMPLES

General Methods and Materials.

a) Reactions in autoclave

The substrate, and the components of the chiral ruthenium (II) catalyst system used in the process of the present invention: bidentate phosphorous-containing ligand, amine and base (if the base is a solid) are weighed (not necessarily anaerobic) in a schlenk flask. With larger quantities of substrate (more than 1.5 mmol) the substrate is

filled directly into the autoclave. The schlenk flask is securated and the solvent (stock solution) is added under anaerobic conditions. The formed suspension is stirred up to the dissolution of the chiral ruthenium (II) catalyst system (ca. 5 min). Then the base solution is added with a securated Hamilton glass syringe and stirred again 5 min if it was not already added as a solid at the beginning. Afterwards the solution is transferred into the securated autoclave standing under vacuum (via capillary and argon pressure). The reaction solution is then heated up to the desired temperature. The desired hydrogen pressure is adjusted.

b) Reactions at normal pressure

The substrate and the components of the chiral ruthenium (II) catalyst system used in the process of the present invention: bidentate phosphorous-containing ligand, amine and base (if the base is a solid) are weighed (not necessarily anaerobic) and given in a temperaturable two neck reaction vessel. This is connected to a dropping funnel containing the solvent (stock solution, anaerobic conditions) and the normal pressure registration equipment. Afterwards this complete system is carefully securated. Furthermore the solution in the dropping funnel is added to the solids in the reaction vessel and the base solution is added to the suspension. Then the argon is replaced with hydrogen (3 x securation with hydrogen). Normal pressure is adjusted by deflating the overpressure over a bubble counter and the measurement is started.

Example 1. Preparation of the enantiomerically enriched thienyl 1-methylpirazoyl carbinol

Table 1: Preparation of the enantiomerically enriched thienyl 1-methylpirazoyl carbinol (variation of standard condition*)

entry	s/c	Diamine	solvent	pressure temperature	time (conversion)	enantiomeric excess
1	50	R-DAIPEN	20 ml isopropanol	8 bar 25 °C	1,5 h (100 %)	90 ee%
2	50	R-DPEN	20 ml isopropanol	8 bar 25 °C	1,5 h (100 %)	86 ee%
3	50	R,R-DACH	20 ml isopropanol	8 bar	4 h	83 ee%

				25 °C	(100 %)	
4	50	R-DPEN	20 ml isopropanol	3 bar 25 °C	3 h (100 %)	85 ee%
5	50	R-DPEN	20 ml isopropanol	20 bar 25 °C	1 h (100 %)	85 ee%
6	50	R-DPEN	20 ml isopropanol	80 bar 25 °C	0.5 h (100 %)	86 ee%
7	100	R-DPEN	20 ml isopropanol	8 bar 30 °C	0.5 h (100 %)	86 ee%
8	100	R,R-DPEN	20 ml t-butanol	8 bar 30 °C	2 h (100 %)	86 ee%
9	100	R,R-DPEN	19 ml t-butanol 1 ml isopropanol	8 bar 30 °C	0.4 h (100 %)	86 ee%
10	125	R,R-DPEN	19 ml t-butanol 1 ml isopropanol	8 bar 30 °C	0.6 h (100 %)	86 ee%
11	500	R,R-DPEN	19 ml t-butanol 1 ml isopropanol	8 bar 30 °C	3.5 h (100 %)	87 ee%
12	100	R,R-DPEN	20 ml isopropanol	1 bar 25 °C	4 h (97 %)	84 ee%
13	100	R,R-DPEN	20 ml t-butanol	1 bar 30 °C	4.5 h (100 %)	88 ee%
14	100	R,R-DPEN	19 ml t-butanol 1 ml isopropanol	1 bar 25 °C	4.5 h (100 %)	88 ee%

* Standard conditions: 0.01 mmol *R,R*-Ru(BINAP); 0.01 mol diamine; 0.5 to 5 mmol ketone; 0.06 mmol *t*-BuOK; 20 ml solvent; 1 - 100 bar H_2; 10 – 45 °C.

Entries 1, 2 and 3

according to method a)

The compound was prepared from 0.5 mmol thienyl 1-methylpyrazoyl ketone

0.01 mmol *R*-Ru(BINAP); 0.01 mmol *R*-DAIPEN, *R,R*-DPEN or *R,R*-DACH;

0.06 mmol *t*-BuOK (60 µl, *t*-BuOK 1.0 M solution in *t*-BuOH);

20 ml isopropanol,

at 25°C and 8 bar H_2.

Conversion: 100 % after 1.5 h with 90 %ee for *R*-DAIPEN,

100 % after 1.5 h with 86 %ee for *R,R*-DPEN and

100 % after 4 h with 83 %ee for *R,R*-DACH.

Entries 4, 5 and 6

according to method a)

The compound was prepared from 0.5 mmol thienyl 1-methylpyrazoyl ketone

0.01 mmol *R*-Ru(BINAP); 0.01 mmol *R,R*-DPEN;

0.06 mmol *t*-BuOK (60 µl, *t*-BuOK 1.0 M solution in *t*-BuOH);

20 ml isopropanol,

at 25°C and 3, 20 or 80 bar H_2.

Conversion: 100 % after 3 h with 85 %ee for 3 bar,

100 % after 1 h with 85 %ee for 20 bar and

100 % after 0.5 h with 86 %ee for 80 bar.

Entries 7, 8 and 9

according to method a)

The compound was prepared from 1 mmol thienyl 1-methylpyrazoyl ketone

0.01 mmol *R*-Ru(BINAP); 0.01 mmol *R,R*-DPEN;

0.06 mmol *t*-BuOK (60 µl, *t*-BuOK 1.0 M solution in *t*-BuOH);

20 ml isopropanol, 20 ml *t*-butanol or 19 ml *t*-butanol and 1 ml isopropanol;

at 30 °C and 8 bar H_2.

Conversion: 100 % after 0.5 h with 86 %ee for 20 ml isopropanol,

100 % after 2 h with 86 %ee for 20 ml *t*-butanol and

100 % after 0.4 h with 86 %ee for 19 ml *t*-butanol and 1 ml isopropanol.

Entries10 and 11

according to method a)

The compound was prepared from 1.25 mmol or 5 mmol thienyl 1-methylpyrazoyl ketone

0.01 mmol *R*-Ru(BINAP); 0.01 mmol *R,R*-DPEN;

0.06 mmol *t*-BuOK (60 µl, *t*-BuOK 1.0 M solution in *t*-BuOH);

19 ml *t*-butanol and 1 ml isopropanol;

at 30 °C and 8 bar H_2.

Conversion: 100 % after 0.6 h with 86 %ee for 1.25 mmol ketone and

100 % after 3.5 h with 87 %ee for 5 mmol ketone.

Entries 12, 13 and 14

according to method b)

The compound was prepared from 1 mmol thienyl 1-methylpyrazoyl ketone

0.01 mmol *R*-Ru(BINAP); 0.01 mmol *R,R*-DPEN;

0.06 mmol *t*-BuOK (60 µl, *t*-BuOK 1.0 M solution in *t*-BuOH);

20 ml isopropanol, 20 ml *t*-butanol or 19 ml *t*-butanol and 1 ml isopropanol;

at 25 °C (30 °C for pure *t*-butanol) and 1 bar H_2.

Conversion: 97 % after 4 h with 84 %ee for 20 ml isopropanol,

100 % after 4.5 h with 88 %ee for 20 ml *t*-butanol and

100 % after 4.5 h with 88 %ee for 19 ml *t*-butanol and 1 ml isopropanol.

The best results concerning the selectivity where obtained with DAIPEN entry 1 and concerning the activity with the 19 to 1 mixture of *t*-butanol and isopropanol at 8 bar and 30 °C, see entry 11.

Example 2. Preparation of the enantiomerically enriched thienyl 1-methylpirazoyl carbinol

Table 2: Preparation of the enantiomerically enriched thienyl 1-methylpirazoyl carbinol. Variation of diphosphine ligand (variation of standard condition*)

entry	s/c	diphosphine ligand diamine	solvent	pressure temperature	time (conversion)	enantiomeric excess
15	200	*R,R*-Ru(BINAP) R-DPEN	19 ml t-butanol 1 ml isopropanol	1 bar 30 °C	5 h (100 %)	86 ee%
16	200	*R,R*-Ru(BINAP) R-DPEN	19 ml t-butanol 1 ml isopropanol	8 bar 17 °C	5 h (100 %)	89 ee%

17	200	*R,R*-Ru(BINAP) R-DPEN	19 ml t-butanol 1 ml isopropanol	8 bar 20 °C	6 h (100 %)	89 ee%
18	200	*R,R*-Ru(BINAP) R-DPEN	19 ml t-butanol 1 ml isopropanol	8 bar 30 °C	2 h (100 %)	88 ee%
19	200	*R,R*-Ru(BINAP) R-DPEN	19 ml t-butanol 1 ml isopropanol	8 bar 40 °C	2 h (100 %)	84 ee%
20	200	*R,R*-Ru(BINAP) R-DPEN	19 ml t-butanol 1 ml isopropanol	8 bar 50 °C	1 h (100 %)	80 ee%
21	200	*R,R*-Ru(BINAP) R-DPEN	19 ml t-butanol 1 ml isopropanol	20 bar 30 °C	0.5 h (100 %)	87 ee%
22	200	*R,R*-Ru(BINAP) R-DPEN	19 ml t-butanol 1 ml isopropanol	50 bar 30 °C	0.25 h (100 %)	86 ee%
23	200	*R*-Ru(CTH-PHOS) R-DPEN	19 ml t-butanol 1 ml isopropanol	8 bar 30 °C	3.5 h (100 %)	74 ee%
24	200	*R,R*-Ru(TolBINAP) R-DPEN	19 ml t-butanol 1 ml isopropanol	8 bar 30 °C	2 h (100 %)	94 ee%
25	5000	*R,R*-Ru(BINAP) R-DPEN	190 ml t-butanol 10 ml isopropanol	50 bar 30 °C	4 h (95 %) 20 h (100 %)	88 ee%
26	10000	*R,R*-Ru(BINAP) R-DPEN	190 ml t-butanol 10 ml isopropanol	50 bar 30 °C	21h (50 %) 45 (64 %)	89 ee%
27[#]	10000	*R,R*-Ru(BINAP) R-DPEN	190 ml t-butanol 10 ml isopropanol	50 bar 30 °C	24 h (92 %) 45 h (97 %)	89 ee%

* Standard conditions: 0.01 mmol diphosphine ligand; 0.01 mol diamine; 2 to 100 mmol ketone; 0.06 mmol *t*-BuOK; solvent; 1 - 50 bar H_2; 17 – 50 °C

[#] 0.24 mmol *t*-BuOK

Entry 15

according to method b)

The compound was prepared from 2 mmol thienyl 1-methylpyrazoyl ketone

0.01 mmol *R,R*-Ru(BINAP); 0.01 mmol *R,R*-DPEN;

0.06 mmol *t*-BuOK (120 µl, *t*-BuOK 0.5 M solution in *t*-BuOH);

19 ml *t*-butanol and 1 ml isopropanol;

at 30 °C and 1 bar H_2.

Conversion: 100 % after 4.5 h with 86 %ee

Entries 16, 17, 18, 19 and 20

according to method a)

The compound was prepared from 2 mmol thienyl 1-methylpyrazoyl ketone

0.01 mmol *R,R*-Ru(BINAP); 0.01 mmol *R,R*-DPEN;

0.06 mmol *t*-BuOK (120 µl, *t*-BuOK 0.5 M solution in *t*-BuOH);

19 ml *t*-butanol and 1 ml isopropanol;

at 17 °C, 20 °C, 30 °C, 40 °C or 50 °C and 8 bar H_2.

Conversion: 100 % after 5 h with 89 %ee at 17 °C,

100 % after 6 h with 89 %ee at 20 °C,

100 % after 2 h with 88 %ee at 30 °C,

100 % after 2 h with 84 %ee at 40 °C and

100 % after 1 h with 89 %ee at 50 °C.

Entries 21 and 22

according to method a)

The compound was prepared from 2 mmol thienyl 1-methylpyrazoyl ketone

0.01 mmol *R,R*-Ru(BINAP); 0.01 mmol *R,R*-DPEN;

0.06 mmol *t*-BuOK (120 µl, *t*-BuOK 0.5 M solution in *t*-BuOH);

19 ml *t*-butanol and 1 ml isopropanol;

at 30 °C and 20 bar or 50 bar H_2.

Conversion: 100 % after 0,5 h with 87 %ee at 20 bar and

100 % after 0,25 h with 86 %ee at 50 bar.

Entries 23 and 24

according to method a)

The compound was prepared from 2 mmol thienyl 1-methylpyrazoyl ketone

0.01 mmol *R*-Ru(CTH-PHOS), *S,S*-Ru(TolBINAP) or *R,R*-Ru(TolBINAP); 0.01 mmol *R,R*-DPEN;

0.06 mmol *t*-BuOK (120 µl, *t*-BuOK 0.5 M solution in *t*-BuOH);

19 ml *t*-butanol and 1 ml isopropanol;

at 30 °C and 8 bar H_2.

Conversion: 100 % after 3.5 h with 74 %ee with *R*-Ru(CTH-PHOS),

100 % after 2 h with 94 %ee with *R,R*-Ru(TolBINAP).

Entries 25, 26 and 27

according to method a)

The compound was prepared from 50 or 100 mmol thienyl 1-methylpyrazoyl ketone

0.01 mmol *R,R*-Ru(BINAP); 0.01 mmol *R,R*-DPEN;

0.06 mmol or 0.24 mmol *t*-BuOK (120 µl or 500 µl, *t*-BuOK 0.5 M solution in *t*-BuOH);

19 ml *t*-butanol and 1 ml isopropanol;

at 30 °C and 50 bar H_2.

Conversion: 95 % after 4 h with 88 %ee and 100 % after 20 h with 50 mmol ketone and 0.06 mmol *t*-BuOK,

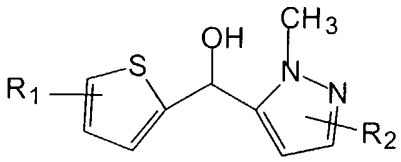
50 % after 21 h with 89 %ee and 64 % after 45 h with 100 mmol ketone and 0.06 mmol *t*-BuOK, and

92 % after 24 h with 89 %ee and 97 % after 45 h with 100 mmol ketone and 0.24 mmol *t*-BuOK.

The best results concerning the selectivity where obtained with *R,R*-Ru(TolBINAP) entry 24 and concerning the activity with the s/c of 5000 (TOF = 1180 h^{-1}) entry 25.

CLAIMS

1. A process for the preparation of an enantiomerically enriched compound of formula (II):

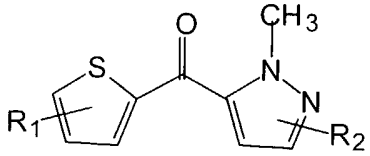


(II)

wherein:

R_1 and R_2 are independently selected from hydrogen, halogen, lower alkyl or aryl;

which comprises the asymmetric hydrogenation of a prochiral ketone of formula (III)



(III)

in the presence of a base and a chiral ruthenium (II) catalyst system comprising at least a bidentate phosphorous-containing ligand and a diamine ligand.

2. A process according to claim 1, wherein the bidentate phosphorous-containing ligand is a bisphosphine ligand comprising a binaphthyl group, preferably selected from the group formed by the stereoisomers of 2,2'-bis(diphenyl-phosphino)-1,1'-binaphtyl (BINAP), TolBINAP and XylBINAP.

3. A process according to claim 1 wherein the diamine is an enantiomerically-enriched 1,2 diamine, preferably selected from the group consisting of 1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine (DAIPEN), 1,2-diphenylethylendiamine (DPEN) or 1,2-diaminocyclohexane (DACH).

4. A process according to claim 3 wherein the diamine is DAIPEN.

5. A process according to claim 3 wherein the diamine is DPEN.

6. A process according to claim 1 wherein the base is selected from alkali metal alcoholates, preferably *t*-butanolate.

7. A process according to claim 1 wherein the base is selected from *t*-BuOK, K_2CO_3, NEt_3 and $AgCF_3SO_3$, preferably *t*-BuOK.

8. A process according to claim 1 wherein the mole ratio base : ruthenium (II) component of the catalyst system is comprised between 10:1 and 1:1, preferably between 6:1 and 2:1, more preferably between about 6:1 and 4:1.

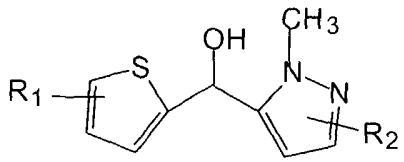
9. A process according to claim 1 wherein the solvent is an alcohol, preferably selected from methanol, isopropanol, t-butanol and their mixtures, more preferably is *t*-butanol.

10. A process according to claim 1 which further comprises an O-alkylation of the enantiomerically enriched compound of formula II.

11. A process according to claim 10 wherein the O-alkylation is carried out on the product of the process as defined in anyone of claims 1-9, without an intermediate separation or purification step.

12. A process according to anyone of claims 1-11 wherein either of R_1 or R_2 is H, preferably both are H.

13. A process for the preparation of an enantiomerically enriched compound of formula (II):

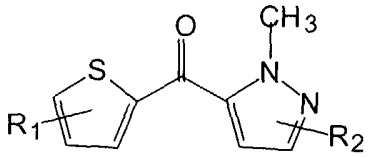


(II)

wherein:

R_1 and R_2 are independently selected from hydrogen, halogen, lower alkyl or aryl;

which comprises the asymmetric hydrogenation of a prochiral ketone of formula (III)



(III)

in the presence of a base and a chiral ruthenium (II) catalyst system comprising at least a bidentate phosphorous-containing ligand selected from TolBINAP and BINAP and a diamine ligand selected from DPEN and DAIPEN.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/014024

A. CLASSIFICATION OF SUBJECT MATTER
C07D409/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 March 2006	30/03/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Helps, I

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/014024

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2005/014024

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