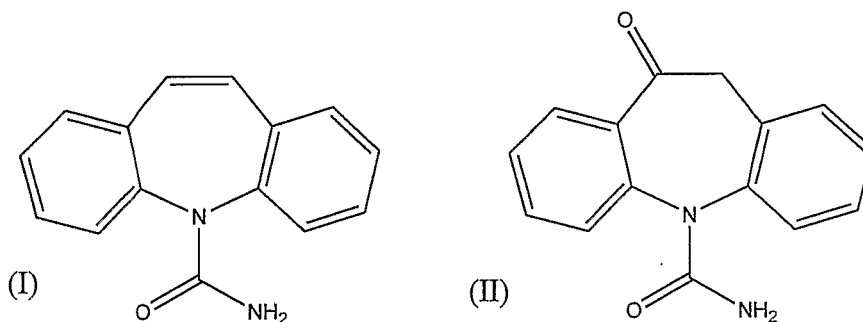


ASYMMETRIC CATALYTIC REDUCTION OF OXCARBAZEPINE

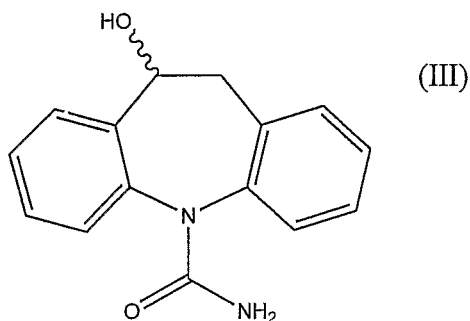
The present invention relates to a process for the asymmetric catalytic reduction of oxcarbazepine (10,11-dihydro-10-oxo-5H-dibenz/b,f/azepine-5-carboxamide).

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Carbamazepine (I) and oxcarbazepine (II) are established first-line drugs used in the treatment of epilepsy:



10 After oral administration to humans, oxcarbazepine (II) is rapidly metabolised to a pharmacologically active 4:1 mixture of the (S) and (R) enantiomers of 10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III):



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WO02/096881 discloses a two-step process for the preparation of racemic (III) from carbamazepine. WO 02/092572 discloses a process for preparing a racemic mixture of (III) from oxcarbazepine and further discloses a process for resolving the (S) and (R)-enantiomers of (III) from the racemic mixture. The enantiomers can be used as intermediates in the preparation of (S)-(-)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide and (R)-(+)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide, two single-isomer drugs that may be used to treat epilepsy and other disorders of the central nervous system (Benes et al, US 5,753,646).

WO 2004/031155 discloses a method for the enantioselective preparation of the (S) and (R)-enantiomers of (III) by asymmetric reduction of oxcarbazepine. The asymmetric reduction is carried out in the presence of a ruthenium catalyst and a hydride source. A suitable catalyst may be formed from $[\text{RuCl}_2(\text{p-cymene})]_2$ and (S,S)-N-(4-toluenesulfonyl)-diphenylethylenediamine (hereinafter referred to as (S,S)-TsDPEN). A mixture of formic acid and triethylamine (in a 5:2 molar ratio) is used as the hydride source. The disclosed process uses a very low substrate: catalyst ratio, i.e. a high amount of catalyst, (e.g. a ratio of 86:1 in example 1). The first major disadvantage of using such a high amount of catalyst is that the residual level of ruthenium metal, a most undesirable contaminant in the product, will be high and difficult to remove, and therefore the product will be unsuitable for use as an active pharmaceutical ingredient (API) or as a late-stage API intermediate. Regulatory guidance for residual metals derived from catalysts exists and the oral concentration limits for ruthenium residues are controlled particularly tightly. The second major disadvantage is that the ruthenium catalyst is expensive. The catalyst system described in WO 2004/031155 is very inefficient, and the cost contribution of the catalyst system alone prevents the process from being economically viable for large-scale manufacturing purposes.

The process disclosed in WO 2004/031155 also uses large quantities of the hydride source (7 equivalents of formic acid and 2.7 equivalents of triethylamine). Commercial sources of the formic acid/triethylamine mixture (triethylammonium formate) are available, but the mixture is expensive. The considerable excess of formic acid used in the process is potentially hazardous as the formic acid can decompose in the presence of the catalyst, causing gradual or spontaneous liberation of carbon dioxide and flammable hydrogen gas as well as causing pressure build-ups inside the reactor vessel. Premature degradation of the hydride source also means that the reduction reaction is slowed down considerably and does not reach full conversion even on prolonged reaction times, making the reaction even less efficient and ultimately providing product of low purity.

In the examples of WO 2004/031155 the crude product obtained by asymmetric reduction of oxcarbazepine is purified by column chromatography over silica gel.

Purification by chromatography on scale is slow, expensive and in many cases impractical due to low throughput. The process disclosed in WO 2004/031155 is not suitable for use on a large scale in terms of efficiency and cannot be regarded as an industrially viable manufacturing process in terms of economy.

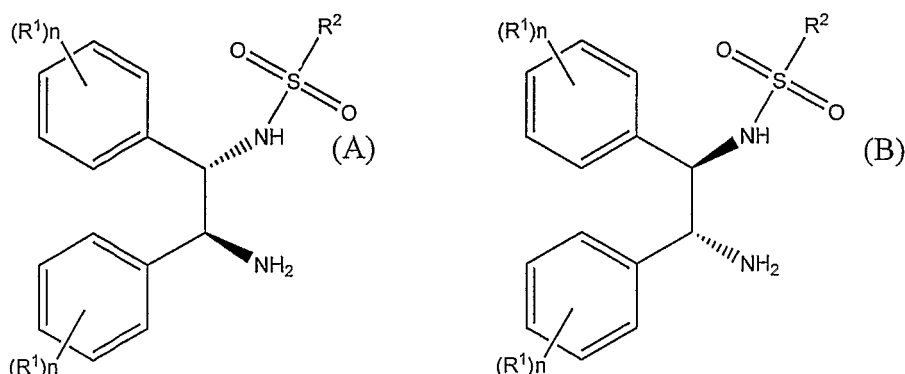
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The present invention thus seeks to provide an improved method for the preparation of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide and (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide, wherein the method is readily amenable to industrial batch-size production. Surprisingly, a process has been devised that can provide high yields of optically pure (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide and (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide, using a greatly reduced quantity of catalyst (i.e. a high substrate/catalyst ratio).

15

Accordingly, the present invention provides a process for preparing (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide, by reduction of oxcarbazepine in the presence of a catalyst and a hydride source, wherein the catalyst is prepared from a combination of $[\text{RuX}_2(\text{L})]_2$ wherein X is chlorine, bromine or iodine, and L is an aryl or aryl-aliphatic ligand, with a ligand of formula (A) or formula (B):

20



25

wherein R^1 is chosen from C_{1-6} alkoxy and C_{1-6} alkyl, n is a number from 0 to 5, and when n is a number from 2 to 5, R^1 can be the same or different, and R^2 is alkyl, substituted alkyl, aryl, substituted aryl, alkaryl or substituted alkaryl;

wherein the hydride source is either $\text{NR}^3\text{R}^4\text{R}^5$ and formic acid, or $[\text{R}^3\text{R}^4\text{R}^5\text{NH}][\text{OOCH}]$ and optionally formic acid, or $[\text{M}][\text{OOCH}]_x$ and formic acid, wherein R^3 , R^4 and R^5 are C_{1-6} alkyl, M is an alkali metal or alkaline earth metal and x is 1 or 2, and wherein during the process a pH from 6.5 to 8 is maintained.

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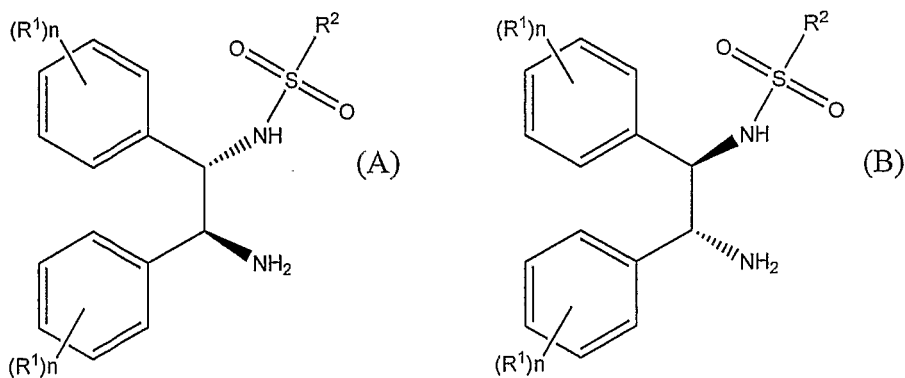
The present invention makes it possible to obtain optically pure (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide. The expression "optically pure" is used to include compounds which have optical purity from 75-100%, preferably from 92-99.5%, more preferably from 96-99.5%.

10

The inventors have found that by controlling the pH of the reaction, it is now possible to achieve high isolated yields of optically pure (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide using acceptably small quantities of catalyst and of the hydride source reagents. The amount of residual ruthenium in the resulting product is very low, making it acceptable for use as an API intermediate. The process is now conveniently operable on a large-scale, and is economically viable, due to the lower cost contribution of the catalyst, simplified isolation procedure and improved yields.

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The active catalyst is prepared from $[\text{RuX}_2(\text{L})]_2$, and a ligand of formula (A) or formula (B):



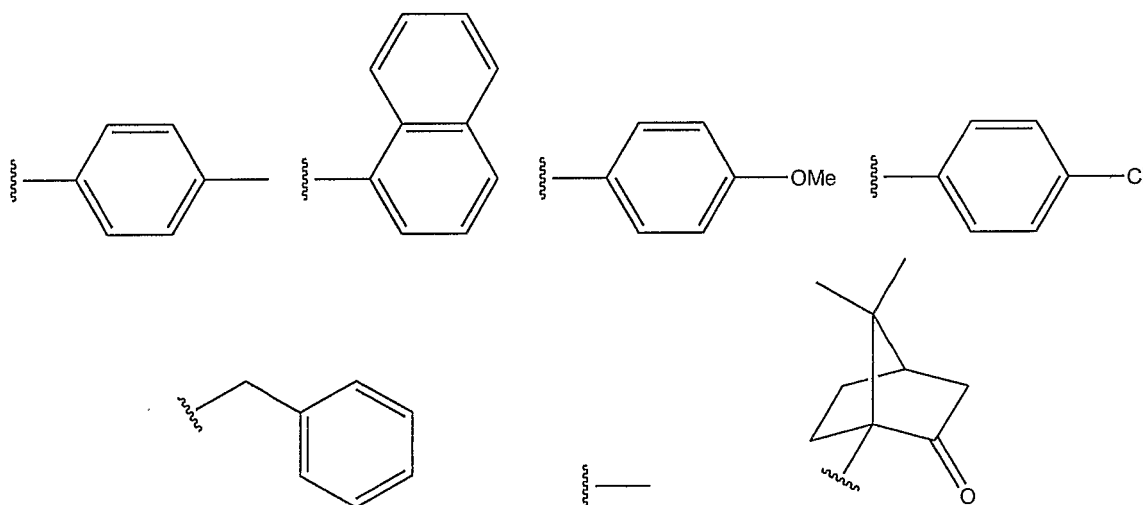
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wherein X is chlorine, bromine or iodine, preferably chlorine; L is an aryl or aryl-aliphatic ligand such as p-cymene (isopropylmethylbenzene), benzene,

hexamethylbenzene or mesitylene, and is preferably p-cymene. R^1 is chosen from C_{1-6} alkoxy and C_{1-6} alkyl, and n is a number from 0 to 5. When n is a number from 2 to 5, R^1 can be the same or different. Preferably, n is either 0 or 1 and when n is 1, R^1 is preferably either a methoxy or methyl group. Most preferably, R^1 is a methoxy group in the para position.

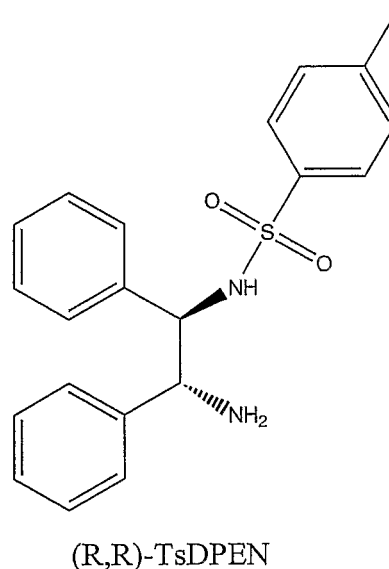
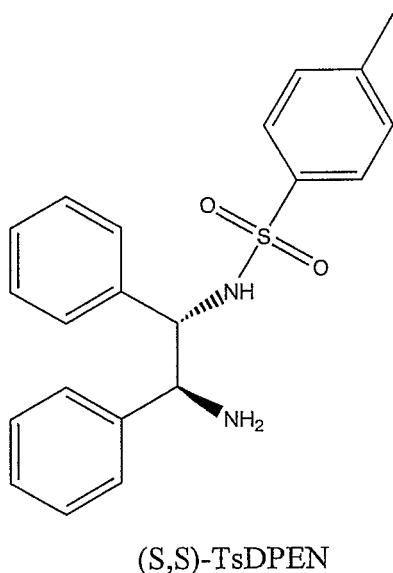
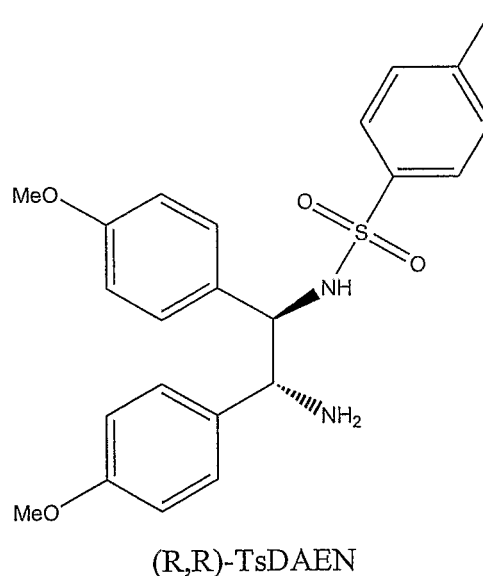
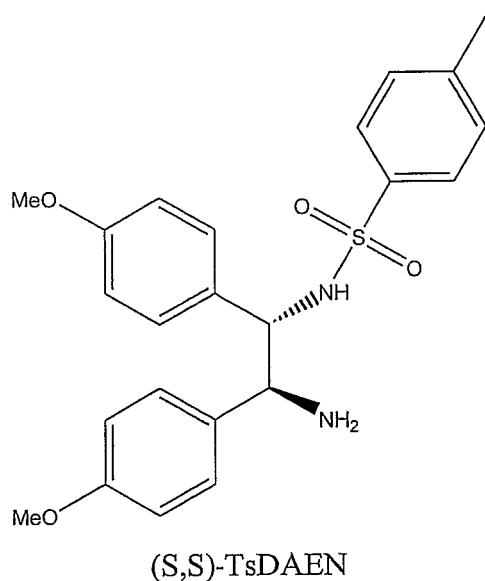
R^2 is an alkyl, substituted alkyl, aryl, substituted aryl, alkaryl or substituted alkaryl group, wherein the alkyl may be straight-chain, branched, cyclic or bridged and the alkyl, aryl or alkaryl groups may be substituted with alkyl, alkoxy, halogen or keto groups. When the R^2 group is an alkyl group, it may suitably contain 1 to 9 carbon atoms. When an alkyl group is substituted on the R^2 group, the alkyl group substituent may suitably contain 1 to 9 carbon atoms. The alkoxy or keto group substituent may suitably contain 1 to 9 carbon atoms. It is preferred that the alkoxy group substituent is methoxy.

Preferred R^2 groups are shown below:



R^2 is preferably a phenyl group substituted by methyl, most preferably a phenyl group substituted by methyl at the para-position. Preferred ligands of formula (A) and (B) are shown below:

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5

The most preferred ligands are (S,S)-TsDAEN and (R,R)-TsDAEN. It has been surprisingly discovered that substitution of the phenyl rings in particular by a methoxy substituent gives rise to a catalyst having greater efficiency for the asymmetric reduction of oxcarbazepine. Accordingly, much lower quantities of this catalyst are required for the preparation of (S) and (R)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide from oxcarbazepine when compared to other ligands.

10

Processes using catalysts formed from ligands of formula (A) provide (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide and processes using

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catalysts formed from ligands of formula (B) provide (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide.

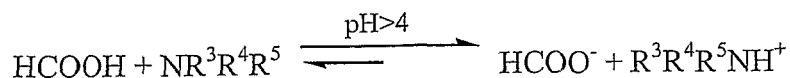
The catalyst is preferably prepared *in situ*, e.g. by combining $[\text{RuX}_2\text{L}]_2$ and the
5 ligand of formula (A) or (B) under inert atmosphere in a solvent such as dimethylformamide (DMF). Figure 1 provides an example of the catalytic cycle that is believed to take place (the hydride source in this example is $[\text{Et}_3\text{NH}][\text{OOCH}]$).

The molar ratio of oxcarbazepine to the ruthenium catalyst (which is equivalent
10 to the molar ratio of oxcarbazepine to ruthenium) is suitably at least 500:1, preferably at least 1000:1, more preferably at least 1500:1. The process can be operated successfully at a molar ratio of oxcarbazepine to the ruthenium catalyst of 2700:1, therefore it is envisaged that the process can be operated with advantage, at oxcarbazepine to ruthenium catalyst ratios of at least 2000:1, more preferably at least 2500:1. It is
15 expected that the process can be operated with oxcarbazepine to ruthenium catalyst ratios of at least 3000:1. Molar ratios lower than 500:1 are not preferred because the precious metal catalyst is expensive and may result in unacceptably high residual ruthenium levels in the isolated product. The process of the invention wherein the pH of the reaction mixture is controlled allows for a significantly improved substrate:catalyst ratios
20 compared to prior art methods wherein the pH is not controlled, e.g. example 1 process of WO 2004/03115 uses an oxcarbazepine to ruthenium ratio of 86:1.

The hydride source is either $\text{NR}^3\text{R}^4\text{R}^5$ and formic acid, or $[\text{R}^3\text{R}^4\text{R}^5\text{NH}][\text{OOCH}]$
25 and optionally formic acid, or $[\text{M}][\text{OOCH}]_x$ and formic acid, wherein R^3 , R^4 and R^5 are C_{1-6} alkyl, M is an alkali metal or alkaline earth metal and x is 1 or 2. R^3 , R^4 and R^5 may be the same or different, but are preferably all the same. The C_{1-6} alkyl groups may be straight-chain, branched or cyclic. Preferably R^3 , R^4 and R^5 are ethyl, propyl or butyl, most preferably ethyl. M is preferably Na, Li or K, most preferably Na. When M is an alkali metal x is 1 and when M is an alkaline earth metal, x is 2.

30 $[\text{R}^3\text{R}^4\text{R}^5\text{NH}][\text{OOCH}]$ reagents, e.g. $[\text{Et}_3\text{NH}][\text{OOCH}]$, are commercially available. $[\text{Et}_3\text{NH}][\text{OOCH}]$ is commonly used in asymmetric reduction reactions but is synthesised from H_2 , CO_2 and NEt_3 in the presence of a ruthenium catalyst and is

therefore expensive, so it is desirable to minimise the use of this type of reagent. When formic acid and $\text{NR}^3\text{R}^4\text{R}^5$ are mixed in a stoichiometric amount, the following acid base equilibrium occurs:



- 5 At low pH, the hydride source exists in its acid form, while at higher pH, it exists in its conjugate base form, a species that participates in the catalytic cycle.

In a first embodiment of the invention, the hydride source is $\text{NR}^3\text{R}^4\text{R}^5$ and formic acid, preferably triethylamine and formic acid. This embodiment avoids the use of the expensive $[\text{R}^3\text{R}^4\text{R}^5\text{NH}][\text{OOCH}]$ reagents. Suitably, the $\text{NR}^3\text{R}^4\text{R}^5$ is added to the reaction mixture at the start of the process. Preferably less than two equivalents of $\text{NR}^3\text{R}^4\text{R}^5$ are added, most preferably about one equivalent. The amount of formic acid that is added to the reaction mixture at the start of the process can be minimised. This is advantageous because the formic acid decomposes to carbon monoxide and hydrogen during the process, and this is potentially hazardous if large quantities of formic acid are used. Suitably less than 1.5 equivalents of formic acid are added to the reaction mixture at the start of the process, preferably less than 1 equivalent, most preferably less than 0.2 equivalents. If less than 1 equivalent of formic acid is added at the start of the process, further formic acid should be added during the course of the reaction, providing about 1-3 equivalents of formic acid in total.

In a second embodiment of the invention, the hydride source is $[\text{R}^3\text{R}^4\text{R}^5\text{NH}][\text{OOCH}]$, preferably $[\text{Et}_3\text{NH}][\text{OOCH}]$, with or without formic acid. Suitably the $[\text{R}^3\text{R}^4\text{R}^5\text{NH}][\text{OOCH}]$ is added to the reaction mixture at the start of the process. Preferably less than two equivalents of $[\text{R}^3\text{R}^4\text{R}^5\text{NH}][\text{OOCH}]$ are used, preferably about one equivalent. Suitably less than 0.5 equivalents of formic acid are added to the reaction mixture at the start of the process, most preferably less than 0.2 equivalents. Further formic acid may be added to the reaction mixture during the course of the reaction.

In a third embodiment of the invention, the hydride source is $[\text{M}][\text{OOCH}]_x$, preferably NaOOCH , and formic acid. Suitably the $[\text{M}][\text{OOCH}]_x$ is added to the

reaction mixture at the start of the process. Preferably less than two equivalents of $[M][OOCH]_x$ are used, preferably about one equivalent. Suitably less than 1.5 equivalents of formic acid are added to the reaction mixture at the start of the process, preferably less than 1 equivalent, most preferably less than 0.2 equivalents. If less than 1
5 equivalent of formic acid is added at the start of the process, further formic acid should be added during the course of the reaction, providing about 1-3 equivalents of formic acid in total.

The process of the invention allows for reduced quantities of hydride source
10 reagents than prior art methods, e.g. the process of WO 2004/03115 wherein pH is not controlled uses seven equivalents of formic acid and 2.7 equivalents of triethylamine. In particular, the process of the present invention minimises the hazards associated with adding large quantities of formic acid to the reaction mixture at the start of the reaction.

15 The pH of the reaction mixture is maintained between 6.5 and 8 during the course of the reaction. Control of pH is essential to provide good conversions and acceptably high product yields, preferably above 85%, whilst using acceptably low quantities of catalyst (e.g. a substrate: catalyst ratio of 500 or more). The pH can be monitored by methods known to those skilled in the art, but a preferred method is to use a Hamilton
20 gel-filled electrode as described in the Examples of the present invention.

The preferred method of controlling the pH is to add formic acid in a controlled manner during the course of the reaction, e.g. by titration. Most preferably, the pH is maintained from 7.0 to 7.8 by the controlled addition of formic acid. In the first
25 embodiment of the invention, wherein the hydride source is $NR^3R^4R^5$ and formic acid, up to 1.5 equivalents of formic acid may be added at the start of the process and then further formic acid may be added as necessary to maintain the pH. However, it is preferred that no formic acid is added to the reaction mixture when the $NR^3R^4R^5$ is added, and all the formic acid is added in a gradual, controlled manner, e.g. dropwise by
30 titration, thus maintaining the pH from 6.5 to 8. It is preferred to add all the formic acid in a gradual, controlled manner because this minimises the hazards associated with decomposition of formic acid. In the second embodiment of the invention, wherein the hydride source comprises $[R^3R^4R^5NH][OOCH]$, it is preferred that no formic acid is

added at the start of the process but that formic acid is subsequently added to maintain the pH. The formic acid is suitably added in a gradual, controlled manner, e.g. dropwise by titration, thus maintaining the pH from 6.5 to 8. In the third embodiment of the invention, wherein the hydride source is $[M][OOCH]_x$ and formic acid, up to 1.5 equivalents of formic acid may be added at the start of the process and then further formic acid may be added as necessary to maintain the pH. However, it is preferred that no formic acid is added to the reaction mixture when the $[M][OOCH]_x$ is added, and all the formic acid is added in a gradual, controlled manner, e.g. dropwise by titration, thus maintaining the pH from 6.5 to 8.

The solubility of oxcarbazepine is appreciably low in most pharmaceutically acceptable process solvents, even at elevated temperatures. Suitable solvents may comprise dimethylformamide (DMF), ethyl acetate (EtOAc), acetonitrile, isopropyl acetate, tetrahydrofuran, 1,2-dichloroethane, dimethoxy ethane and/or water. It is preferred that the solvent comprises at least one polar aprotic solvent such as DMF or acetonitrile because these solvents are miscible with both organic and inorganic phases. Surprisingly, standard non-deoxygenated reagent grade solvents are suitable for use in the process of the present invention. A preferred solvent system for the process of the present invention is a mixture of two or more solvents selected from DMF, EtOAc, acetonitrile and water. In the first embodiment of the invention wherein the hydride source is $NR^3R^4R^5$ and formic acid, the solvent suitably comprises 0-25% DMF, 0-25% water and 75-95% EtOAc or 0-25% acetonitrile, 0-25% water and 75-95% EtOAc, preferably 0-20% DMF, 5-20% water and 80-90% EtOAc. The most preferred solvent is 10% DMF, 10% water and 80% EtOAc. In the second embodiment of the invention wherein the hydride source is $[R^3R^4R^5NH][OOCH]$ with or without formic acid, the solvent suitably comprises 5-25% DMF and 75-95% EtOAc, 5-25% acetonitrile and 75-95% EtOAc, 5-25% DMF and 75-95% water, or 5-25% acetonitrile and 75-95% water. In the third embodiment of the invention, wherein the hydride source is $[M][OOCH]_x$ and formic acid the solvent suitably comprises 0-25% DMF, 0-25% water and 75-95% EtOAc or 0-25% acetonitrile, 0-25% water and 75-95% EtOAc, preferably 0-20% DMF, 5-20% water and 80-90% EtOAc.

In a particular embodiment of the process, the reduction takes place in the presence of a phase transfer catalyst. Suitable phase transfer catalysts include quaternary alkyl ammonium halides, such as for example Bu₄NBr. The ratio of phase transfer catalyst to catalyst is suitably from 0.01 to 0.5, preferably about 0.1.

The reaction can be carried out at different temperatures and pressures. Suitably the reaction is carried out at atmospheric pressure and at the reflux temperature of the preferred solvent system. An external temperature of 100-120°C, more preferably 105-110°C is appropriate for the most preferred solvent systems.

The reaction time will depend on key factors such as the ratio of oxcarbazepine to catalyst. Preferably the reaction should be completed in less than 36 hours, more preferably in less than 24 hours and high yields have been achieved by applying the process of the present invention in reaction times of less than 24 hours at oxcarbazepine to catalyst ratios even greater than 2000:1.

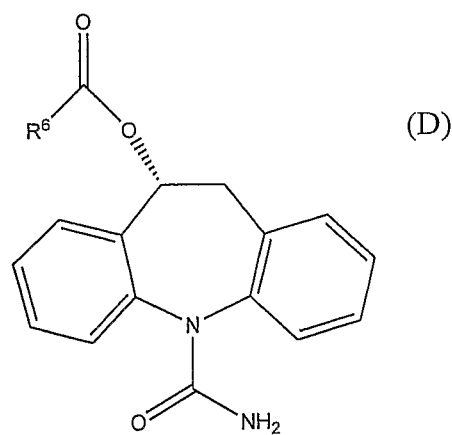
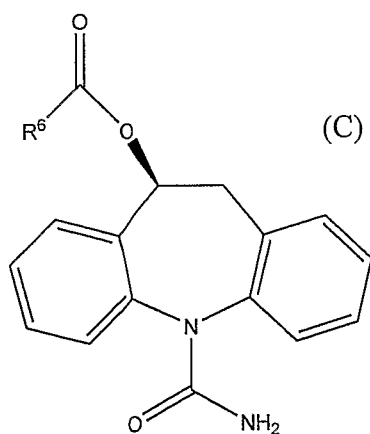
In the first embodiment of the invention wherein the hydride source is NR³R⁴R⁵ and formic acid, the product may spontaneously precipitate from the reaction mixture as it cools from reflux temperature. A suitable solvent, preferably methyl *tert*-butyl ether (MTBE) is added to the reaction mixture before filtration. In the second embodiment of the invention wherein the hydride source is [R³R⁴R⁵NH][OOCH] with or without formic acid, the product may be isolated by precipitating the crude product from suitable solvent mixtures, preferably either methanol/water or methanol/MTBE at 0-5°C. The work-up procedures are particularly simple compared to prior art methods such as those disclosed in WO 2004/031155 wherein the work-up procedure requires neutralisation of excess formic acid, extraction, drying, solvent evaporation and flash chromatography. These procedures are unsuitable for large-scale manufacture. In the present invention the simple work-up procedures result in acceptably low residual ruthenium content in the isolated product, consistent with its intended use as a final intermediate in the manufacture of APIs.

In an alternative embodiment, the (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-

dibenz/b,f/azepine-5-carboxamide may be precipitated by removing the reaction solvent while adding water to maintain the reaction volume at a substantially constant level. The reaction solvent, which is preferably ethyl acetate, may be removed by distillation. The distillation temperature is preferably at least 60°C. Typically the weight of water replacing the reaction solvent may be in the range 80-120%, more preferably 90-110% of the weight of the solvent removed. In this embodiment, the removal of the precipitated (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide may subsequently be isolated by filtration, and can be further purified, preferably by reslurrying in a solvent, which is preferably ethyl acetate and re-filtration.

Another advantage of the present invention is that it is possible to run the reaction with a high substrate concentration e.g. 0.5-1.5M, so that the volume efficiency of the reaction is very good. This is especially relevant when considering large-scale manufacturing.

The (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide produced according to the process of the present invention may be used as an API and formulated into finished pharmaceutical products, or may be converted by further chemical transformation to another API, e.g. (S)-(-)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide may be provided by esterification of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide. The present invention further provides a process for preparing a compound of formula (C) or (D)



wherein R⁶ is hydrogen, alkyl, halogenalkyl, aralkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aryl or pyridyl; comprising a first step, which is a process for the production of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide according to the invention,
 5 and a second step, wherein the (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide is acylated. The compounds produced in accordance with this process may be optically pure, wherein optically pure means compounds which have optical purity from 75-100%, preferably from 92-99.5%, more preferably from 96-
 10 99.5%.

R⁶ may be straight or branched C₁₋₁₈ alkyl, which may be substituted with halogen (F, Cl, Br or I). It may also be cycloalkyl (a cyclic C₃-C₆ saturated group) or aryl (unsubstituted phenyl or phenyl substituted by alkoxy, halogen or nitro group).
 15 Preferably R⁶ is CH₃. Compounds of formula (C) and (D) are further described in US 5,753,646. Suitable acylation methods are described in US 5,753,646 and WO 02/092572, e.g. (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide may be reacted with acetylchloride or acetic anhydride in dichloromethane to give (S)-(-)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide.

20 The appropriate stereoisomers of the following additional compounds may also be converted from (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide using an appropriate process, as described in US 5,753,646:

- (1) 10-benzoyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- 25 (2) 10-(4-methoxybenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (3) 10-(3-methoxybenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (4) 10-(2-methoxybenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-
 30 carboxamide
- (5) 10-(4-nitrobenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide

- (6) 10-(3-nitrobenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (7) 10-(2-nitrobenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- 5 (8) 10-(4-chlorobenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (9) 10-(3-chlorobenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (10) 10-(2-acetoxybenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- 10 (11) 10-propionyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (12) 10-butyryloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (13) 10-pivaloyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (14) 10-[(2-propyl)pentanoyloxy]-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- 15 (15) 10-[(2-ethyl)hexanoyloxy]-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (16) 10-stearoyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (17) 10-cyclopentanoyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- 20 (18) 10-cyclohexanoyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (19) 10-phenylacetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (20) 10-(4-methoxyphenyl)acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- 25 (21) 10-(3-methoxyphenyl)acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (22) 10-(4-nitrophenyl)acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- 30 (23) 10-(3-nitrophenyl)acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (24) 10-nicotinoyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (25) 10-isonicotinoyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide

(26) 10-chloroacetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide

(27) 10-bromoacetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide

(28) 10-formyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide

(29) 10-ethoxycarbonyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-

5 carboxamide

(30) 10-(2-chloropropionyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-

carboxamide

The invention is now described by reference to examples, which are not intended
10 to be limiting thereof.

**Example 1: Asymmetric Reduction of Oxcarbazepine using NEt_3 and pH-
controlled addition of HCOOH**

15 In a 2L 5-necked round bottom flask, oxcarbazepine was charged (635mmol, 169g), the flask was fitted with two water reflux condensers connected to a Schlenk line (two reflux condensers were used to secure two escape routes for CO_2 and H_2 gases evolving from the reaction), a burette for titration and a Hamilton gel-filled electrode fitted through a hollow GL25 screw cap equipped with a PTFE/silicone ring. To the
20 starting material under N_2 flow, EtOAc (480mL, undegassed, HPLC grade), H_2O (48mL, undegassed, HPLC grade) and Et_3N (1.1eq., 699mmol, 97.5mL, undegassed, Fluka, 99.9% pure) were added with the aid of a graduated cylinder. The catalyst (formed separately *in situ* in a 50mL Schlenk tube under N_2 flow by stirring $[\text{RuCl}_2(p\text{-cymene})]_2$ (0.1588mmol, 97.2mg) and (*S,S*)-TsDAEN (2.2eq. with respect to the metal dimer precursor, 0.3493mmol, 159mg) in DMF (13mL, degassed, anhydrous) at room
25 temperature for 10-15min. was injected. The Schlenk tube was rinsed with small portions of the remaining DMF (5x7mL) and injected to the reaction mixture. The solvent combination at this point was 10% DMF-10% H_2O -80%EtOAc (v/v/v) and the substrate concentration before titration was 1.1M. The round bottom flask was placed in
30 an oil bath preheated at 105°C and the reaction mixture magnetically stirred at reflux ($T_{\text{oil bath}} = 105^\circ\text{C}$, internal $T = 72\text{-}77^\circ\text{C}$). Once the reaction mixture started refluxing, the reaction pH was approximately 8.8. At this point the titration/slow addition with 12.5 M HCOOH solution in 20%DMF/EtOAc was started. The pH was slowly brought to 7.4

and then maintained constant at this value over 12hrs by slowly adding the HCOOH solution. The HPLC conversion after 15hrs was 99%. Further stirring up to 20hrs resulted in the formation of a white precipitate and has not consumed the remaining 1% oxcarbazepine. A total of approximately 3.7eq. HCOOH with respect to the starting material was consumed during the reaction. The overall substrate/product concentration at the end of the reaction was 0.86 M. After 20hrs, the heating was stopped and the reaction mixture was stirred and allowed to cool down slowly. When the temperature of the oil bath reached approximately 80°C, 500mL MTBE was added to the reaction mixture and allowed to cool to room temperature under stirring. The reaction mixture was stirred at 0-5°C for approximately 30min, filtered and the precipitate was washed repeatedly with cold portions of MTBE until the filtrate was colourless. The resulting white precipitate was dried in the air, then under high vacuum, affording a white powder: 95% isolated yield (152g). HPLC: 99.6% product, 97.8% e.e., 0.4% oxcarbazepine.

Due to the fact that under these reaction conditions (10%DMF-10%H₂O-80%EtOAc, 1.1eq. Et₃N and HCOOH) the product crystallises out at the refluxing temperature, no solvent was evaporated during the work-up. The very low solubility of the product in MTBE, allows not only further precipitation of the starting material, but also it aids the purification/removal of residual ruthenium, DMF and reagents by washing the filtrate with copious amounts, without a loss in the isolated yield. The ruthenium level in the product was between 5-50ppm.

Example 2: Asymmetric Reduction of Oxcarbazepine using [Et₃NH][OOCH] and pH-controlled addition of HCOOH

In a 500mL 4-necked round bottom flask, oxcarbazepine was charged (159mmol, 40g), the flask fitted with a water reflux condenser connected to a Schlenk line, a burette for titration and a Hamilton gel filled electrode fitted through a hollow GL25 screw cap with a PTFE/silicone ring. The flask was flushed with N₂ for approximately 30min. To the starting material under N₂ flow, EtOAc (78mL, degassed, anhydrous), [Et₃NH][OOCH] commercially available from Fluka (1.07 eq., 170mmol, 25mL, undegassed, Fluka) were added via a syringe. The catalyst (formed separately *in situ* in a

20mL Schlenk tube by stirring $[\text{RuCl}_2(p\text{-cymene})]_2$ (0.0265mmol, 16.2mg) and (*S,S*)-TsDAEN (2.2 eq. with respect to the metal dimer precursor, 0.0582mmol, 25mg) in DMF (5mL, degassed, anhydrous) at room temperature for 10-15min. was injected. The Schlenk tube was rinsed with small portions of the remaining DMF (5x3mL) and injected to the reaction mixture. The solvent combination at this point was 20%DMF-80%EtOAc (v/v) and the oxcarbazepine concentration before titration was 1.3M. The round bottom flask was placed in an oil bath preheated at 105°C and the reaction mixture was magnetically stirred at reflux ($T_{\text{oil bath}} = 105^\circ\text{C}$). Once the reaction mixture started refluxing, the reaction pH was approximately 6.8. The reaction mixture slowly turned purple and the pH started increasing as HCOOH from the triethylammonium formate was consumed. When the pH reached 7.4-7.45 the titration/slow addition with 12.5 M HCOOH solution in 20%DMF/EtOAc was started. The pH was maintained at pH = 7.4 over 12hrs by slowly adding the HCOOH solution. After 17hrs the reaction mixture was clear purple, with some catalyst decomposition observed on the walls of the flask. The HPLC conversion after 17hrs was 98%. At this point the pH of the solution was 7.8 and addition of more HCOOH solution was continued at 7.7. Further stirring up to 23hrs led to 99% conversion. Approximately 4.7eq. HCOOH with respect to the starting material was consumed during the reaction. After 23hrs, the heating was stopped and the reaction mixture was stirred and allowed to cool down. The reaction mixture was concentrated, 100mL MTBE added and the solvent removed again. 15mL MeOH was added and the white paste refluxed for about 5min and then 250mL MTBE added slowly to this refluxing mixture. The resulting mixture was stirred at reflux for 30min, cooled to RT, then to 0-5°C and stirred for 30min. The mixture was filtered cold and washed with cold portions of MTBE until the filtrate was colourless (8x50mL). The resulting white precipitate was dried in the air, then under high vacuum, affording a white powder: 94% isolated yield (37.9g); HPLC: 99.5% product, 97.8% e.e., 0.5% oxcarbazepine. The ruthenium level in the product was between 5-50ppm.

Comparison 1a: Asymmetric reduction with and without pH Control (Hydride source is NEt_3 and HCOOH)

Reactions were carried out using a method similar to that of example 1. The substrate/catalyst ratio was 2000 and the solvent was 20% H_2O /EtOAc. The ligand was

(S,S)-Ts-DAEN. In example 3, 1eq. NEt_3 and 1eq. HCOOH were added to the reaction mixture at the start of the reaction. Further HCOOH was added throughout the course of the reaction to maintain a pH of 7.4. In comparative example 1, 4.4eq. Et_3N and 4eq. HCOOH were pre-mixed in H_2O and added to the reaction mixture in EtOAc at the beginning of the reaction. Table 1 shows the results of example 3 and comparative example 1:

Table 1

	Hydride source	Time (h)	Alcohol (%)	e.e (%)
Example 3	1eq. of NEt ₃ and 1eq. of HCOOH added at start of reaction. Further 1.7eq. of HCOOH added during the course of the reaction, maintaining the pH at 7.4.	2	22	98.8
		4	33	98.7
		6	46	98.8
		8	57	98.5
		26	82	98.3
		33	82	98.3
Comparative Example 1	Mixture of 4.4eq. of NEt ₃ and 4eq. HCOOH in H ₂ O/EtOAc added at the start of the reaction.	21	31	96.8

The yield of the pH controlled reaction (example 3) was much better than the yield of the reaction in which pH was not controlled (comparative example 1), despite the fact that higher quantities of hydride source reagents were used.

Comparison 1b: Asymmetric reduction with and without pH Control (Hydride source is [Et₃NH][OOCH] or [Et₃NH][OOCH] and HCOOH)

Reactions were carried out using a method similar to that of example 2. The substrate/catalyst ratio was 1000 and the solvent was 10% DMF/EtOAc. The ligand was Ts-DPEN rather than Ts-DAEN. 20g of oxcarbazepine were used instead of 40g. [Et₃NH][OOCH] was added to the reaction mixture at the start of the reaction and no further HCOOH was added. Table 2 shows how the results of two comparative examples using different quantities of [Et₃NH][OOCH]:

Table 2

	[Et ₃ NH][OOCH] (eq)	Time (h)	pH	Conversion (%)	Enantiomeric excess (%)
Comparative Example 2	5	0	6.95	0	-
		22	8.6	100	97.7
Comparative Example 3	2	0	6.7	-	-
		0.15	6.8	-	-
		0.5	7.55	-	-
		1.5	8.25	-	-
		2	8.86	-	-
		3	8.85	-	-
		5	8.65	-	-
		6	8.6	-	-
		19	8.22	47	98.5

5 equivalents of the expensive reagent [Et₃NH][OOCH] provided 100% conversion after 22 hours, whereas less than 50% conversion was achieved with only 2 equivalents of the reagent. The pH of the reaction mixture increased during the course of the reaction.

The reaction was repeated on a 10g scale using a substrate/catalyst ratio of 1500:1 and a 20% DMF/EtOAc solvent. In comparative examples 4 and 5, 5 equivalents of [Et₃NH][OOCH] were used and no further HCOOH was added. In example 4, only one equivalent of [Et₃NH][OOCH] was used but further HCOOH was added during the course of the reaction to maintain the pH at 7.4. Table 3 shows the results of comparative examples 4 and 5 and example 4:

Table 3

	Ligand	Hydride Source	Time (h)	Conversion (%)	Enantiomeric Excess (%)
Comparative Example 4	(S,S)- TsDPEN	5 eq. [Et ₃ NH][OOCH]	25	98	97
Comparative Example 5	(S,S)- TsDAEN	5 eq. [Et ₃ NH][OOCH]	20	97	96.9
Example 4	(S,S)- TsDAEN	1 eq. [Et ₃ NH][OOCH] plus HCOOH to maintain pH 7.4	7	99	97.8

A comparison of comparative examples 4 and 5 with example 4 shows that by controlling the pH by addition of HCOOH, a much smaller quantity of the expensive reagent [Et₃NH][OOCH] can be used, and the reaction reaches almost complete conversion in 7 hours rather than 20-25 hours.

Comparison 2: Asymmetric Reduction using a Variety of Ligands

10

The activity of catalysts comprising the (S,S)-TsDAEN and (S,S)-TsDPEN ligands was compared at a 20-40g scale. The catalysts were generated in situ by stirring [RuCl₂(p-cymene)]₂ and either (S,S)-TsDAEN or (S,S)-TsDPEN for 5-10 minutes in DMF before addition to oxcarbazepine and 1.07 equivalents of [Et₃NH][OOCH]. 12.5M HCOOH solution in 20% DMF/EtOAc was injected slowly at pH=7.4. The ratio of oxcarbazepine to catalyst was 3000:1. Table 4 shows the results for Examples 5 and 6 (using (S,S)-TsDAEN) and example 7 (using (S,S)-TsDPEN):

20

Table 4

	Scale (g)	ligand	Time (h)	Conversion (%)	Enantiomeric excess (%)
Example 5	40	(S,S)-TsDAEN	23	99	98.1
Example 6	25	(S,S)-TsDAEN	4	55	98.2
			6	69	98.3
			8	77	98
			26	97	97.9
Example 7	20	(S,S)-TsDPEN	5	47	98.4
			6	54	98.2
			7	64	98.3
			8	77	98
			23	83	98
			26	85	97.8
			30	86	97.8

The (S,S)-TsDAEN examples show significantly better conversion than the (S,S)-TsDPEN example and show similar enantioselectivity.

5

Comparison 3: Asymmetric reduction of Oxcarbazepine using a phase transfer catalyst

10 Table 5 shows the results of three asymmetric reduction reactions wherein a phase transfer catalyst was used in addition to the ruthenium catalyst. In each reaction, the catalyst was generated *in situ* by adding $[\text{RuCl}_2(\text{p-cymene})]_2$ and a ligand to EtOAc and stirring. (NB (R,R)-TsDTEN has the same structure as (R,R)-TsDPEN except that the phenyl groups are substituted by tolyl groups). The phase transfer catalyst was 0.1
 15 equivalents of Bu_4NBr . The hydride source was 2 equivalents of $[\text{Et}_3\text{NH}][\text{OOCH}]$ and additional formic acid was slowly added to the reaction mixture during the course of the reaction. The ratio of oxcarbazepine to catalyst was 2000:1 and the external reaction temperature was 110°C. The conversion in example 9, wherein the ligand was (R,R)-

TsDAEN was significantly better than the conversion in examples 8 and 10, wherein the ligands were (S,S)-TsDPEN and (R,R)-DTEN.

Table 5

	Ligand	Time (h)	Conversion (%)	Enantiomeric excess (%)
Example 8	(S,S)-TsDPEN	6	58	98 (S)
Example 9	(R,R)-TsDAEN	6	70	98.2(R)
Example 10	(R,R)-TsDTEN	6	60	97.8 (R)

5

Example 3: Acetylation of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide

10 (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (500g), obtained via asymmetric transfer hydrogenation as described above, and 4-(*N,N*-dimethylamino)pyridine (4g) were suspended in dichloromethane (5.07L). Pyridine (210mL) was added to the suspension. The reaction mixture was heated to reflux whereupon acetic anhydride (240mL) was added dropwise. The resulting yellowish-
15 brown solution was stirred for 2 hours and then cooled to 30°C.

The reaction mixture was then quenched by the addition of sulphuric acid. After stirring for 10 min, the layers were separated. The organic layer was washed twice with saturated aqueous sodium bicarbonate solution and then water. Approximately half of the
20 dichloromethane was then removed by evaporation and isopropanol (5 L) was added to the mixture which was then left to stand overnight. Further solvent was evaporated (approximately 1.5L) and the resulting slurry was cooled to approximately 3°C. After 3 hours the solid was filtered off, washed with cold isopropanol and then dried under vacuum overnight. The dried solid was suspended in isopropanol (6.5 L) and the
25 resulting white slurry was heated to reflux. Once a solution was obtained heating was stopped and the reaction mixture was stirred for ~ 1 hr at 1-5 °C. Solids were isolated by

filtration, washed with cold isopropanol and dried under vacuum to yield 524.2 g of white solid, 90 % yield, 99.96 % chemical purity, (R)-isomer below the limit of detection.

5 Residual ruthenium content was found to be less than 2ppm. According to the regulatory guidelines, the oral concentration limit is 5ppm.

Example 4: Asymmetric reduction of Oxcarbazepine using higher oxcarbazepine:
catalyst ratio

10

This reduction described in example 1 was carried out on oxcarbazepine (357mmol, 90 g) using [RuCl₂(p-cymene)]₂ (0.066mmol, 40.4mg) and (S,S)-TsDAEN (0.145mmol, 61.9 mg) using four times the quantity of water. The reaction was complete in 27 hours .

15

Ethyl acetate was distilled from the batch while maintaining the original batch volume by the addition of water (dropwise). Temperature was maintained above 60°C during the distillation. Approximately 1/3 into the distillation the product started to precipitate.

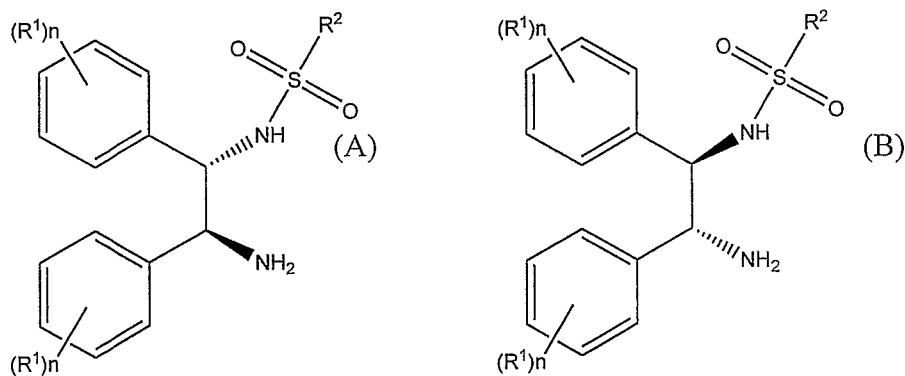
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The mixture was cooled to 5°C, held at that temperature for one hour and then filtered. The filter cake was washed with water. The wet cake was then reslurried in ethyl acetate (350 mL) and heated to reflux for 0.5 hours. It was then cooled to 5°C and held at that temperature for 1 hour. The mixture was then filtered and the recovered
25 solids with ethyl acetate (120 mL). Drying under high vacuum afforded an off-white powder: 88% isolated yield (79.8g): HPLC: 99.8% product, 98.4% e.e., 0.09% oxcarbazepine

It will be appreciated that the invention described above may be modified.

Claims

1. A process for preparing (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide, by reduction of oxcarbazepine in the presence of a catalyst and a hydride source, wherein the catalyst is prepared from a combination of $[\text{RuX}_2(\text{L})]_2$ wherein X is chlorine, bromine or iodine, and L is an aryl or aryl-aliphatic ligand, with a ligand of formula (A) or formula (B):



wherein R^1 is chosen from C_{1-6} alkoxy and C_{1-6} alkyl, n is a number from 0 to 5, and when n is from 2 to 5, R^1 can be the same or different, and R^2 is alkyl, substituted alkyl, aryl, substituted aryl, alkaryl or substituted alkaryl;

wherein the hydride source is chosen from $\text{NR}^3\text{R}^4\text{R}^5$ and formic acid, or $[\text{R}^3\text{R}^4\text{R}^5\text{NH}][\text{OOCH}]$ and optionally formic acid, or $[\text{M}][\text{OOCH}]_x$ and formic acid, wherein R^3 , R^4 and R^5 are C_{1-6} alkyl, M is an alkali metal or alkaline earth metal and x is 1 or 2,

and wherein during the process a pH from 6.5 to 8 is maintained.

2. A process according to claim 1, wherein X is chlorine.

3. A process according to claim 1 or claim 2, wherein L is p-cymene.

4. A process according to any preceding claim, wherein n is 1 and R^1 is a methoxy group or a methyl group.

5. A process according to claim 4, wherein n is 1 and R¹ is a methoxy group or a methyl group in the para position.

6. A process according to any preceding claim wherein the ligand of formula (A) or formula (B) is (S,S)-N-(4-toluenesulfonyl)-di(methoxyphenyl)ethylenediamine, ((S,S)-TsDAEN), or (R,R)-N-(4-toluenesulfonyl)-di(methoxyphenyl)ethylenediamine, ((R,R)-TsDAEN).

7. A process according to any preceding claim, wherein the molar ratio of oxcarbazepine to the ruthenium catalyst is at least 500:1

8. A process according to claim 7, wherein the molar ratio of oxcarbazepine to the ruthenium catalyst is at least 1500:1.

9. A process according to claim 7, wherein the molar ratio of oxcarbazepine to the ruthenium catalyst is at least 2500:1.

10. A process according to any preceding claim, wherein the hydride source is NR³R⁴R⁵ and formic acid.

11. A process according to claim 10, wherein less than two equivalents of NR³R⁴R⁵ and less than 1 equivalent of formic acid are added to the reaction mixture at the start of the process.

12. A process according to any one of claims 1 to 9, wherein the hydride source is [R³R⁴R⁵NH][OOCH] and optionally formic acid.

13. A process according to claim 10, wherein less than two equivalents of [R³R⁴R⁵NH][OOCH] and less than 0.5 equivalents of formic acid are added to the reaction mixture at the start of the process.

14. A process according to any one of claims 1 to 9, wherein the hydride source is $[M][OOCH]_x$ and formic acid.

15. A process according to claim 14, wherein less than two equivalents of $[M][OOCH]_x$ and less than 1 equivalent of formic acid are added to the reaction mixture at the start of the process.

16. A process according to any preceding claim wherein R^3 , R^4 and R^5 are ethyl, propyl or butyl.

17. A process according to any preceding claim, wherein the pH is maintained from 6.5 to 8 by adding formic acid in a controlled manner during the course of the reaction.

18. A process according to claim 17, wherein the pH is maintained from 7.0 to 7.8 by adding formic acid in a controlled manner during the course of the reaction.

19. A process according to any preceding claim, wherein the reduction takes place in a solvent, wherein the solvent comprises at least one polar aprotic solvent.

20. A process according to claim 19, wherein the solvent comprises dimethylformamide or acetonitrile.

21. A process according to claim 10 claim 11, claim 14 or claim 15, wherein the reduction takes place in a solvent consisting of 0-25% DMF, 0-25% water and 75-95% EtOAc or 0-25% acetonitrile, 0-25% water and 75-95% EtOAc.

22. A process according to claim 12 or claim 13, wherein the reduction takes place in a solvent consisting of 5-25% DMF and 75-95% EtOAc, 5-25% acetonitrile and 75-95% EtOAc, 5-25% DMF and 75-95% water, or 5-25% acetonitrile and 75-95% water.

23. A process according to any preceding claim wherein the process is carried out under reflux conditions.

24. A process according to any preceding claim, wherein the reduction takes place in the presence of a phase transfer catalyst and the phase transfer catalyst is a quaternary alkyl ammonium halide.

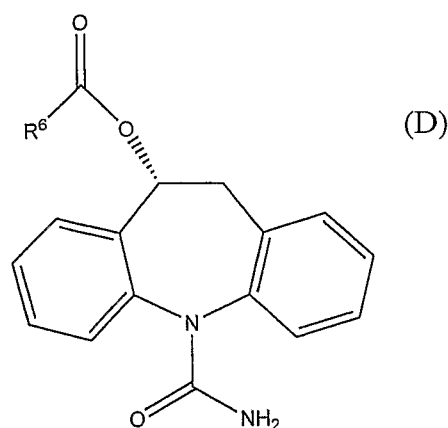
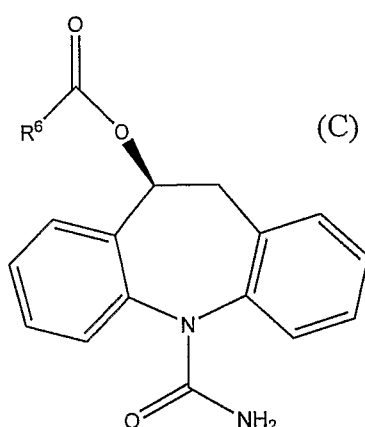
25. A process according to any preceding claim, wherein the (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide is isolated either by addition of methyl *tert*-butyl ether (MTBE) and filtration, or by precipitation from either methanol/water or methanol/MTBE at 0-5°C.

26. A process according to any one of claims 1 to 24, wherein the (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide is precipitated by removing the reaction solvent while adding water to maintain the reaction volume at a substantially constant level.

27. A process according to claim 26, wherein the precipitated (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide is isolated by filtration followed by reslurrying in ethyl acetate and filtration.

28. A process according to any preceding claim wherein the (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide has an optical purity in the range 92-100%.

29. A process for preparing an compound of formula (C) or (D)



wherein R^6 is hydrogen, alkyl, halogenalkyl, aralkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aryl or pyridyl; comprising a first step, which is a process for the production of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide according to any preceding claim, and a second step, wherein the (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide or (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide is acylated.

30. A process for preparing (S)-(-)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide comprising a first step, which is a process for the production of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide according to any one of claims 1 to 28, and a second step wherein the (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide is acylated.

31. A process for preparing (R)-(+)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide comprising a first step, which is a process for the production of (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide according to any one of claims 1 to 28, and a second step wherein the (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide is acylated.