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(54) Title: PROCESS FOR THE ASYMMETRIC OXIDATION OF ORGANIC COMPOUNDS WITH PEROXIDES IN THE PRESENCE OF A CHIRAL ACID CATALYST

(57) **Abstract**: The present invention relates to a process for the asymmetric oxidation of nucleophilic organic compounds, particularly metal-free, with peroxide compounds in the presence of a chiral Bronsted acid catalyst. In one detail, the present invention relates to a process for enantioselective sulfoxidation of thiocompounds with peroxide compounds in the presence of a chiral imidodiphosphate catalyst. In another detail, the present invention relates to a process for enantioselective sulfoxidation of thiocompounds with peroxide compounds in the presence of a chiral phosphoric acid catalyst.

Process for the asymmetric oxidation of organic compounds with peroxides in the presence of a chiral acid catalyst

The present invention relates to a process for the asymmetric oxidation of *nucleophilic* organic compounds, particularly metal-free, with peroxide compounds in the presence of a chiral Brønsted acid catalyst. Said process is distinct from known reactions which require an *electrophilic* organic compound for a reaction with a peroxide compound in the presence of a chiral Brønsted acid catalyst (Angew. Chem. Int. Ed. **2010**, 49, 6589-6591; Angew. Chem. Int. Ed. **2008**, 47, 8112-8115). The present invention exploits peroxide compounds as direct electrophilic sources of oxygen atom, while in the prior art peroxide compounds are exploited as nucleophiles.

In one detail, the present invention relates to a process for enantioselective sulfoxidation of thiocompounds with peroxide compounds in the presence of a chiral imidodiphosphate catalyst. In another detail, the present invention relates to a process for enantioselective sulfoxidation of thiocompounds with peroxide compounds in the presence of a chiral phosphoric acid catalyst.

Asymmetric oxidations of organic compounds, in particular those including oxygen atom transfer to the substrate, are highly valuable transformations for accessing chiral molecules. Both, enzymes and numerous artificial catalysts employ metals to facilitate these types of reactions.

Hydrogen peroxide is next to oxygen the most attractive oxidant, with the waste produced after the reaction being only water. It is produced on a million ton scale each year, and widely available in the form of safe aqueous solutions. Unsurprisingly, significant efforts have been undertaken to utilize H_2O_2 for oxidations in organic chemistry. In metal catalysis it is used as a terminal oxidant with actual oxidizing intermediates being, for example, metal-oxo and metal-peroxo species.

Chiral sulfoxides are widely used as intermediates, auxiliaries, and ligands in modern organic synthesis, and they are also a common and perhaps underappreciated substructure of many biologically active molecules and pharmaceuticals such as Omeprazole, Esomeprazole and Modafinil (R. Bentley, *Chem. Soc. Rev.* **2005**, *34*, 609 – 623; J. Legros, J. R. Dehli, C. Bolm, *Adv. Synth. Catal.* **2005**, *347*, 19 – 31). Of the methods for the synthesis of enantioenriched sulfoxides (e.g. resolution, substrate or reagent-controlled synthesis), the enantioselective catalytic oxidation of sulfides is the most efficient and straightforward approach. Since the first catalytic system was reported in 1984 by Kagan (P. Pitchen, E. Duñach, M. N. Deshmukh, H. B. Kagan, *J. Am. Chem. Soc.* **1984**, *106*, 8188 – 8193) and Modena (F. DiFuria, G. Modena, R. Seraglia, *Synthesis* **1984**, 325 – 326), using modified Sharpless epoxidation catalysts, several elegant metal-based enantioselective sulfoxidation reactions of sulfides have been developed during the last three decades.

However, such metal-based systems usually suffer from some limitations like metal contamination, over-oxidation, a limited substrate scope etc. In contrast to the significant progress in the metal catalysis, the development of organocatalytic methods is still in its infancy, although organocatalysis has experienced an explosive progress and expansion during the last decade.

Among metal-free methods, high enantioselectivity has been achieved by using chiral imines or oxaziridiniums, but these transformations require stoichiometric amounts of the chiral reagents and the corresponding catalytic systems are relatively less efficient. Considering the importance of optically pure sulfoxides in synthetic and medicinal chemistry, a general, metal-free, and highly enantioselective catalytic sulfoxidation reaction of sulfides is highly desirable.

Thus, the inventors have developed a novel and metal-free method for the enantioselective oxidation of sulfides such as thioethers. Though it is quite difficult to activate simple thioethers via covalent or H-bonding activation, which are two most common activation models in organocatalysis, due to the lack of a site or a functional group to establish an efficient interaction between the organic catalysts and the sulfides, the inventors have found out that a viable approach was given by the activation of oxidants and that an asymmetric version of the sulfoxidation reaction was achieved by using chiral Brønsted acids like binol-derived phosphoric acids or imidodiphosphates in combination with peroxide compounds like hydrogen peroxide or alkylhydroperoxide.

The inventors found out that peroxide moiety could be activated by bifunctional chiral Brønsted acids through formation of two hydrogen bonds as shown in Figure 1.

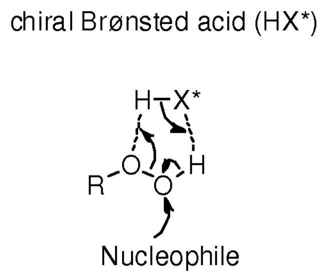
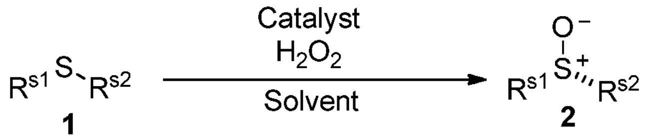


Figure 1.

The present invention is therefore directed to a process for preparing sulfoxides by enantioselectively oxidizing thiocompounds with hydrogen peroxide or alkyl hydroperoxide in the presence of a Brønsted acid catalyst, such as chiral imidodiphosphates or phosphoric acids, for example, a binol-derived phosphoric acid, as represented in the following reaction scheme:



In a broader scope, the invention is directed to oxidizing a compound $X^sR^X_n$ with a peroxide compound ROOH in the presence of a chiral imidodiphosphate catalyst having the general formula (I) below to obtain $X^s(\text{-O})R^X_n$ - including the representations of $R^x_nX^{s+}\text{–}O^-$ and $R^x_nX^s\text{=O}$ - and R^pOH,

$$X^sR^X_n \xrightarrow[\text{Solvent}]{\text{Catalyst}\quad R^pOOH} X^s(\text{-O})R^X_n + R^pOH$$

wherein:

- X^s can be selected from S, Se, P or N,
- R^X can be the same or different on X and may be selected from $\text{–}NR^Y_2$, $\text{-}SR^Y$, $\text{-}OR^Y$, $\text{-}OSiR^Y_3$, C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, each hydrocarbon optionally being

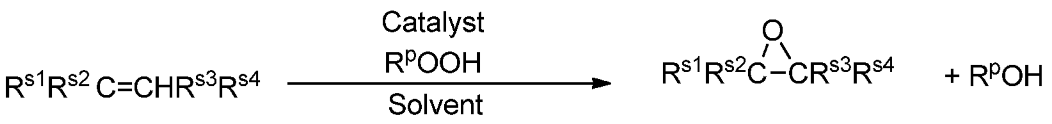
substituted by one or more groups selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl or heterosubstituents,

- n is 2 when X^s is S or Se, and n is 3 when X^s is P or N,
- R^p and R^Y may be independently selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, each hydrocarbon optionally being substituted by one or more groups selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl or heterosubstituents.

In principle $X^sR^X_n$ can be any S, Se, P or N compound which can be oxidized to give an S^+–O^-, Se^+–O^-, P^+–O^- or N^+–O^- compound as a final product or as an intermediate which is further reacted in the reaction.

In the simplest form, the peroxide compound is hydrogen peroxide, but aliphatic or aromatic hydroperoxides, aliphatic or aromatic percarboxylic acids or mixtures thereof might be used as well.

In a further embodiment, the present invention is directed to a process for oxidizing an alkylene compound to an epoxy compound and optionally, further hydrolyzing said epoxy compound to a hydroxyl compound or, depending on the substituent on the alkylene unit, to an alpha-hydroxy-carbonyl-compound.



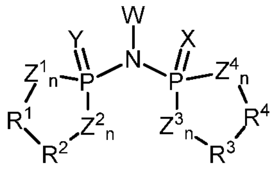
In said reaction scheme, R^{s1} to R^{s4} may have the meaning as given before for R^X. In principle any double bond which can be oxidized to give an epoxide, as a final product or as an intermediate which is further reacted in the reaction.

In a still further embodiment, the present invention is directed to a process for oxidizing an alpha-hydrogen-carbonyl-compound to an alpha-hydroxy-carbonyl-compound.

$$R^{s1}R^{s2}\,CH\text{-}(C{=}O)R^{s3} \xrightarrow[\text{Solvent}]{\substack{\text{Catalyst} \\ R^{p}OOH}} R^{s1}Rs^{2}\,COH\text{-}(C{=}O)R^{s3} \quad + R^{p}OH$$

In said reaction scheme, R^{s1} to R^{s3} may have the meaning as given before for R^X and R^p may have the meaning as given before. In principle any alpha-hydrogen-carbonyl-compound which can be oxidized to give an alpha-hydroxy-carbonyl-compound, as a final product or as an intermediate which is further reacted in the reaction. In addition $(CO)R^{s3}$ could be replaced by another electron-withdrawing groups having a tautomerizable double bond adjacent to the CH-site, such as $–NO_2$, -CN.

In embodiments of the inventive processes, the present invention makes use of chiral imidodiphosphates and derivatives thereof having the general formula (I), which have been described in EP12150663.8, as follows:



(I)

wherein:

X and Y may be, independently from each other, the same or different and represent O, S, Se and NR^N,

Z^1 to Z^4 may be, independently from each other, the same or different and represent O, S and NR^N,

n stands for 0 or preferably 1,

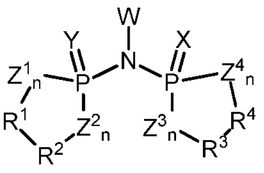
W may be substituent being capable of forming a covalent or ionic bond with the imidodiphosphate moiety,

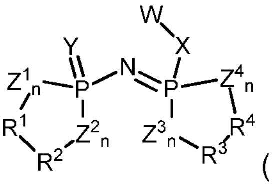
R^1 to R^4 may be, independently from each other, the same or different and may be each an aliphatic, heteroaliphatic, aromatic or heteroaromatic group, each optionally being further substituted by one or more heterosubstituents, aliphatic, heteroaliphatic, aromatic or heteroaromatic groups whereby R^1 and R^2 are forming a ring system with Z^1 and Z^2 and R^3 and R^4 are forming a ring system with Z^3 and Z^4, respectively, and

R^N may be selected from hydrogen, C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, each hydrocarbon optionally being substituted by one or more groups selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl or heterosubstituents,

including its tautomeric and ionic forms, and derivatives thereof.

In the following, it is to be understood that the above formula (I) comprises its tautomeric forms as represented by the formulae (Ia) or (Ib)


(Ia)


(Ib)

wherein X, Y, Z^1 to Z^4, n, W, R^1 to R^4 and R^N have the meaning as defined above. In the following, it is to be understood that any of the formulae (II), (III), (IV) and (V) below comprises its respective tautomeric forms as represented by formula (Ia) or formula (Ib).

In the present application, the expression "imidodiphosphates" is to be understood to comprise derivatives thereof, wherein one or more of the oxygen atoms of the imidodiphosphate moiety is replaced by S, Se, NR^N as defined above.

In the above formula (I) and the derived formulae below, it is to be understood that any tautomeric form of the inventive chiral imidodiphosphates as well as any charged form thereof including any anionic form is to be comprised by the representation of said formula. It is also to be understood that imidodiphosphates could possess inherent chirality even if all of the groups R^1 to R^4 are achiral groups.

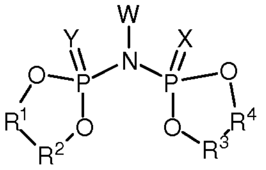
In the above formulae (I), R^1 to R^4 may be selected each from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, each hydrocarbon optionally being substituted by one or more groups selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl or heterosubstituents.

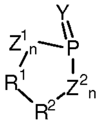
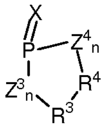
In the above formula (I), W is a substituent being capable of forming a covalent or ionic bond with the imidodiphosphate moiety such as hydrogen, -OH, halogen, a metal such as Li, Na, K, Rb, Cs, Be, Mg, Ca, Sr, Ba, Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Y, Zr, Mo, Ru, Rh, Pd, Ag, W, Re, Os, Ir, Pt, Au, Al, Pb, La, Sm, Eu, Yb, U, or a cationic organic group as exemplified in Scheme 2 below, R^w or a substituted silicon such as $-SiR^IR^{II}R^{III}$, wherein R^w, R^I, R^{II} and R^{III} may be same or different and each stand for hydrogen, halogen, C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, each hydrocarbon optionally being substituted by one or more groups selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl or a heterosubstituent.

The expression "partially arene-hydrogenated forms thereof" is to be understood that in case that the aromatic structure comprises more than one aromatic cycle such as for naphthalene, at least one aromatic cycle, one aromatic cycle remaining, might be partially or fully hydrogenated.

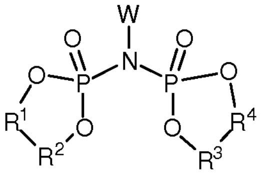
The anionic form may be complemented by any cation for forming an ion pair.

In one embodiment of the above formulae (I), Z^1 to Z^4 represent O, n is 1 and the other definitions are as given before for formula (I), as represented by formula (II):


(II)

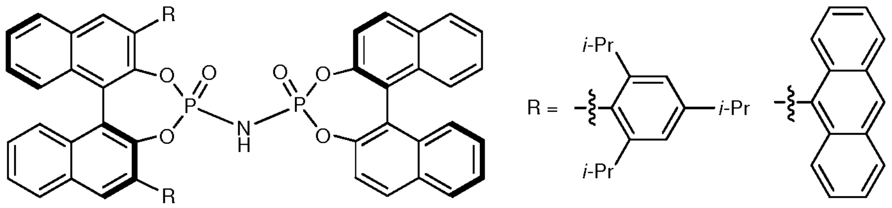
In such formulae (I) and (II), the moiety  or  might be a five to ten-membered ring structure of (R^1, R^2, Z^1, Z^2 and –PY-) or (R^3, R^4, Z^3, Z^4 and –PX-), respectively.

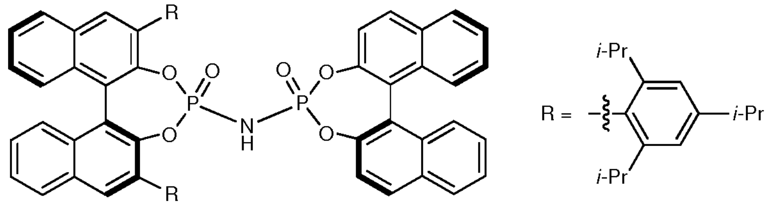
In one embodiment of the compounds of formula (II), X and Y represent O and the other definitions are as given before for formulae (I), as represented by formula (III):

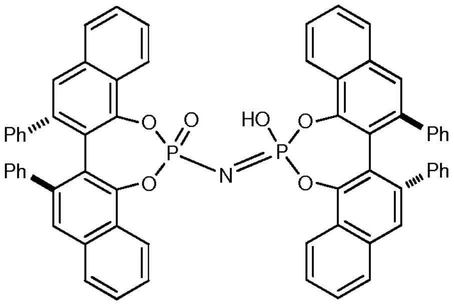

(III)

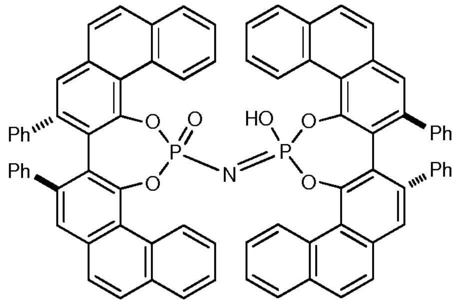
In such formula (III), at least one of (R^1 and R^2) and (R^3 and R^4) may form a ring structure derived from a bridged aromatic structure such as biphenyl optionally substituted, BINOL, TADDOL, VAPOL, SPINOL, 1,1′-binaphthalene, 1,1′-bianthracene, 1,1-biphenanthrene, as well as the partially arene-hydrogenated forms such as 8H-BINOL, each of said rings systems optionally being substituted by one or more substituents selected from heterosubstituents, C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, each hydrocarbon optionally being substituted by one or more heterosubstituents. In such formula (III), the ring structure formed by (R^1 and R^2) or (R^3 and R^4) may be the same or different.

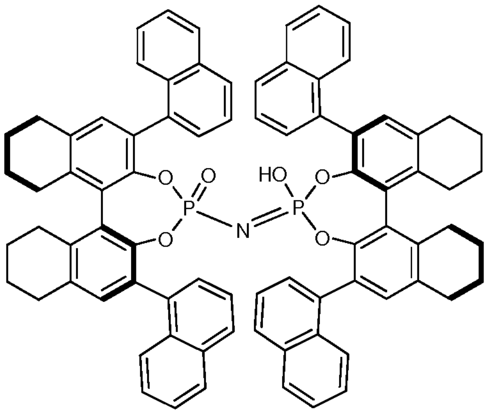
Examples of said compound having the formula (III) and prepared by the inventors are shown below:



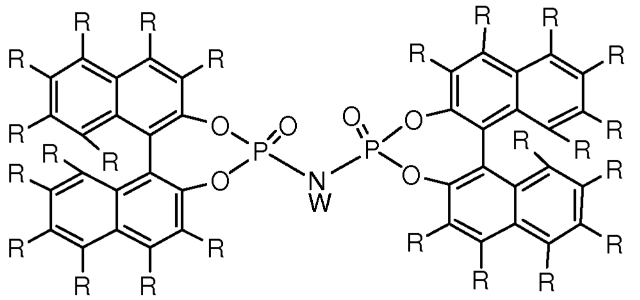








In a further embodiment, the compounds of formula (I) may be represented by formula (IV):



(IV)

In said formula (IV), the substituent R may be the same or different on each position and may each stand for hydrogen, a heterosubstituent, C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, each hydrocarbon optionally being substituted by one or more groups selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl or a heterosubstituent.

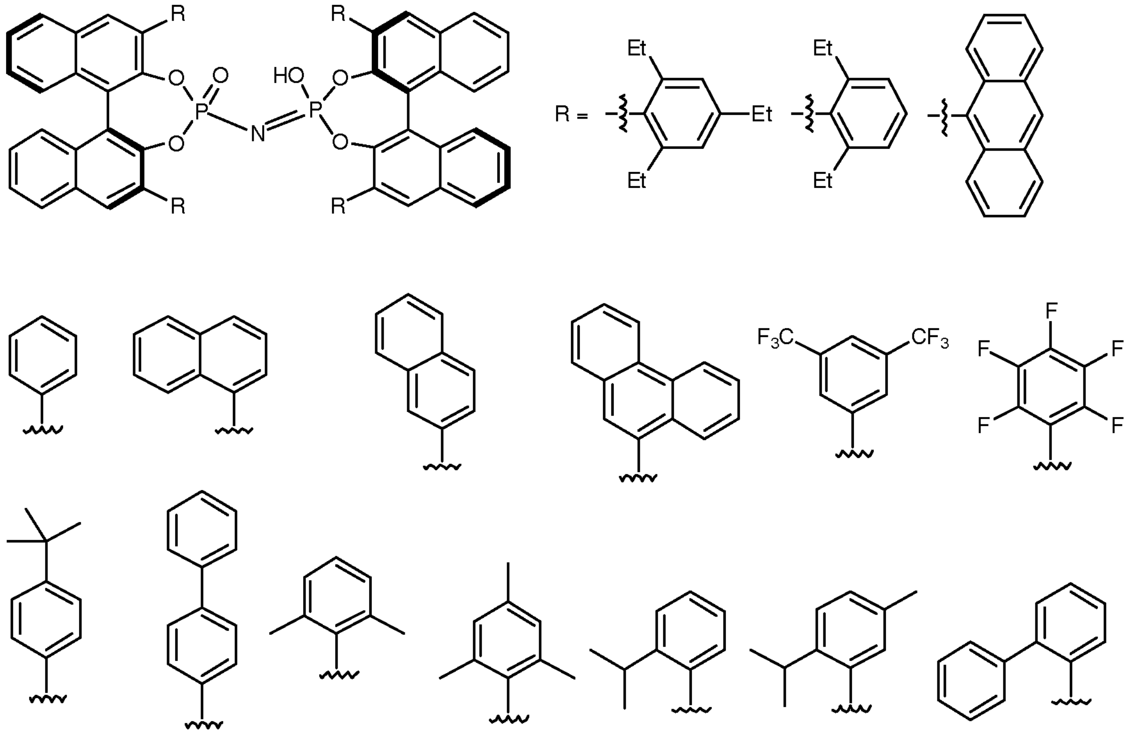
In said formula (IV), W is defined as given before for formula (I).

The substituents on the ring structure proximal to the –Z-P- bond, such as the –O-P-bond, are preferably bulky groups and may be selected from the definitions for R^N or heterosubstituents.

In the inventive processes, the chiral imidodiphosphates having the general formula (II), (III) or (IV) are preferably used.

Basically, any chiral groups are possible as chiral groups for the inventive compounds. If the other group in each case is not chiral, the groups R^1 to R^4 are any organic group which may be saturated or unsaturated, linear, cyclic or heterocyclic, aromatic and/or heteroaromatic.

Examples of said compound having the formula (IV) and prepared by the inventors are shown below:



In organic synthesis, particularly in the synthesis of pharmaceutical active compounds, chiral compounds are frequently used as catalysts in order to obtain the desired product in a high enantiomeric purity or diastereomeric purity.

It has been found that the compounds according to the invention are well suited as catalysts for enantioselective synthesis. Here, they function as chiral Brønsted acids or the conjugated bases thereof as chiral anions in enantioselective catalyses directed by counterions.

The following definitions for the individual substituents/groups apply equally as follows.

A heterosubstituent as defined according to the invention can be selected from OH, F, Cl, Br, I, CN, NO_2, SO_3H, a monohalogenomethyl group, a dihalogenomethyl group, a trihalogenomethyl group, $CF(CF3)_2$, SF_5, amine bound through N atom, -O-alkyl (alkoxy), -O-aryl, $-O-SiR^S_3$, $-S-R^S$, $-S(O)-R^S$, $-S(O)_2-R^S$, -COOH, CO_2-R^S, -amide, bound through C or N atom, formyl group, $C(O)-R^S$, COOM, where M may be a metal such as Na or K. R^S_3 may be, independently from each other, the same or different and may be each an aliphatic, heteroaliphatic, aromatic or heteroaromatic group, each optionally being further substituted by one or more heterosubstituents, aliphatic, heteroaliphatic, aromatic or heteroaromatic groups.

Aliphatic hydrocarbons including alkyl, alkenyl and alkinyl may comprise straight-chain, branched and cyclic hydrocarbons.

Heteroaliphatic is a hydrocarbon including alkyl, alkenyl and alkinyl which may comprise straight-chain, branched and cyclic hydrocarbons with one or more carbon atoms substituted with a heteroatom.

In more detail, C_1-C_{20}-Alkyl can be straight chain or branched and has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms. Alkyl might be C_1-C_6-alkyl, in particular methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, likewise pentyl, 1-, 2- or 3-methylpropyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl. Substituted alkyl groups are trifluoromethyl, pentafluoroethyl and 1,1,1-trifluoroethyl.

Cycloalkyl might be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Alkenyl might be C_2-C_{20} alkenyl. Alkinyl might be C_2-C_{20} alkinyl.

Said unsaturated alkenyl- or alkinyl groups can be used for linking the inventive compounds to a carrier such as a polymer to serve for an immobilized catalyst.

Halogen is F, Cl, Br or I.

Alkoxy is preferably C_2-C_{10} alkoxy such as methoxy, ethoxy, propoxy, *tert*-butoxy etc.

C_3-C_8-Heterocycloalkyl having one or more heteroatoms selected from among N, O and S is preferably 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8-3,4-dihydro-2H-benzo-1,4-oxazinyl.

Optionally substituted means unsubstituted or monosubstituted, disubstituted, trisubstituted, tetrasubstituted, pentasubstituted, or even further substituted for each hydrogen on the hydrocarbon.

Aryl might be phenyl, naphthyl or biphenyl.

Arylalkyl might be benzyl.

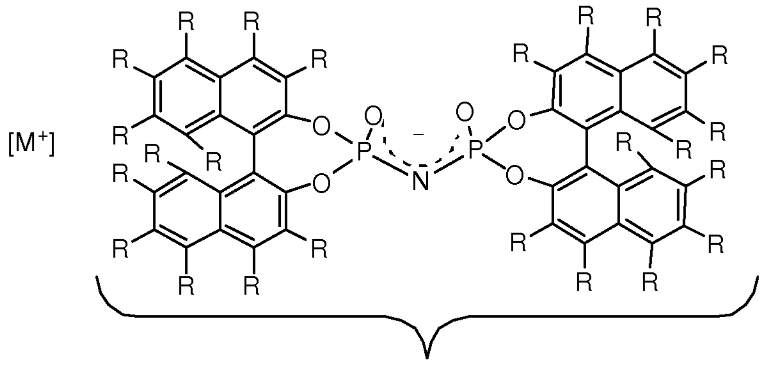
Heteroaryl having one or more heteroatoms selected from among N, O and S is preferably 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, also preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-Indolyl, 4- or 5-

isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl, also preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4- or -5-yl or 2,1,3-benzoxadiazol-5-yl.

In a preferred embodiment of the present invention as for example shown in formula (IV), at least one of R proximal to the -O-P- bond is not hydrogen and may be selected from among methyl, ethyl, isopropyl, cyclohexyl, cyclopentyl, phenyl, 2,4,6-triisopropylphenyl, 2,4,6-triethylphenyl, 2,6-diethylphenyl, 2,6-diethylphenyl, 2-isopropyllphenyl, 5-methyl-2-isopropyllphenyl, mesityl, 9-phenanthryl, 9-anthracenyl, ferrocenyl, N-(perfluorophenyl)acetamide, N-(4-chlorophenyl)acetamide, N-(naphthalen-1-yl)acetamide, N-benzhydrylacetamide, N-(2,6-diisopropylphenyl)acetamide, 1-anthracenyl, corannulene, porphyrin, 1-naphthyl, 2-naphthyl, 4-biphenyl, 3,5-(trifluoromethyl)phenyl, 2,6-dimethylphenyl, tert-butyl, tris-methylsilyl, *tert*-butydimethylsilyl, phenyldimethylsilyl, methyldiphenylsilyl, tris-mesitylsilyl, tris-phenylsilyl, 4-nitrophenyl and 2,6-methyl-4-butylphenyl, trifluoromethyl, unbranched (linear) and branched (C_1-C_{12})-perfluoroalkyls, 3,4,5-trifluorophenyl, 1,3-bis(perfluoropropan-2-yl)phenyl, 1,3-bis(perfluorobutyl)phenyl and/or pentafluorophenyl and also chloride, iodide, fluoride, COOH, $B(OH)_2$, $B(alkyl)_2$, $B(O\text{-}alkyl)_2$, B(pinacol), BF_3X where X = Na or K, OTf. The other groups are preferably hydrogen.

The compounds according to the invention can be converted in process steps which are well known per se to those skilled in the art into organic salts, metal salts or metal complexes. In one possible embodiment, the imidodiphosphates are reacted with an appropriate metal salt, for example with the carbonate of the appropriate metal. Examples of organic salts, metal salts and metal complexes are shown in the following Scheme 1 for formula (V):

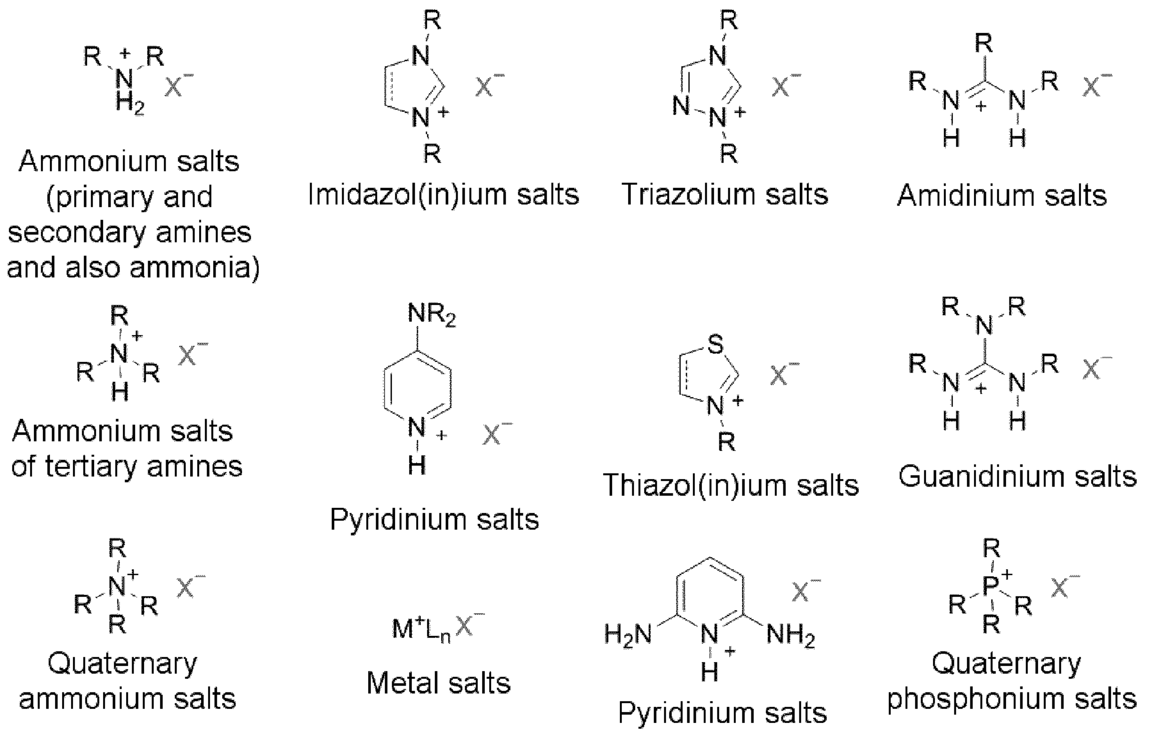
Scheme 1: General examples of metal salts and metal complexes of the imidodiphosphates V.



(V) X^-

In Scheme 1, any metals or organic cations, e.g. tertiary ammonium ions, can be represented by M. Even though the compounds are shown as salts in scheme 1, the precise structure with metals is not known; they can also have the structure of metal complexes. The formulation metal salts or metal complexes is therefore used for the purposes of the present invention. The metal compounds are not restricted to particular metal compounds or complexes. Suitable metal compounds are derived from Li, Na, K, Rb, Cs, Be, Mg, Ca, Sr, Ba, Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Y, Zr, Mo, Ru, Rh, Pd, Ag, W, Re, Os, Ir, Pt, Au, Al, Pb, La, Sm, Eu, Yb, U.

Scheme 2: Examples of possible cations M^+X^-



In other embodiments of the inventive processes, the present invention makes use of chiral acids and derivatives thereof as catalysts which are known in the state of art such as those disclosed in:

EP 1623971.

Hoffmann, S., Seayad, A. M. & List, B. Angew. Chem. Int. Ed. 44, 7424-7427 (2005).

Xu, F. et al. J. Org. Chem. 75, 8677-8680 (2010).

Čorić, I., Müller, S. & List, B. J. Am. Chem. Soc. 132, 17370-17373 (2010).

Nakashima, D. & Yamamoto, H. J. Am. Chem. Soc. 128, 9626-9627 (2006).

Akiyama, T., Itoh, J., Yokota, K. & Fuchibe, K. Angew. Chem. Int. Ed. 43, 1566-1568 (2004).

Uraguchi, D. & Terada, M. J. Am. Chem. Soc. 126, 5356-5357 (2004).

Storer, R. I., Carrera, D. E., Ni, Y. & MacMillan, D. W. C. J. Am. Chem. Soc. 128, 84-86 (2006).

Rowland, G. B. et al. J. Am. Chem. Soc. 127, 15696-15697 (2005).

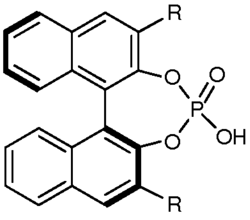
Akiyama, T., Saitoh, Y., Morita, H. & Fuchibe, K. Adv. Synth. Catal. 347, 1523-1526 (2005).

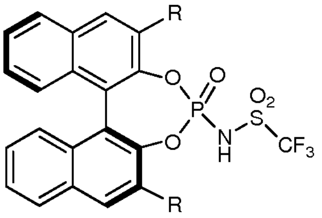
Müller, S., Webber, M. J. & List, B. J. Am. Chem. Soc., 133, 18534-18537 (2011).

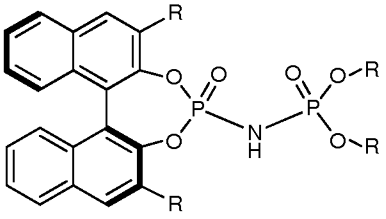
García-García, P., Lay, F., García-García, P., Rabalakos, C. & List, B. Angew. Chem. Int. Ed. 48, 4363-4366 (2009).

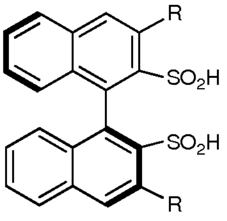
Vellalath, S., Čorić, I. & List, B. Angew. Chem. Int. Ed. 49, 9749-9752 (2010).

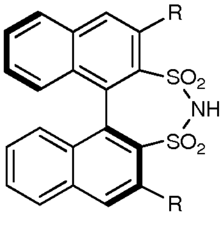
Such chiral acid catalyst to be used for the asymmetric oxidation without the need of an intermediate activation reaction making use of an activation reagent such as a coupling agent like carbodiimide here can be selected from chiral phosphoric acids, sulfonic acids, carboxylic acids, bisulfonimides, triflyl phosphoramides, phosphinyl phosphoramides and derivatives thereof preferably on the basis of a aromatic structure as exemplified above for formula (III) such as BINOL, TADDOL, VAPOL, SPINOL, as well as the partially arene-hydrogenated forms thereof such as 8H-BINOL, and comprises a reactive site represented by a formula [-(P,S,C)=O][(-NHR^E,-OH] – wherein R^E has the meaning of an electron-withdrawing group, as represented exemplarily as follows:

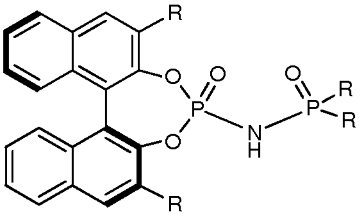


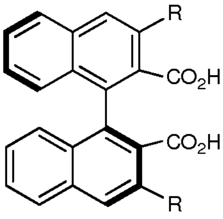


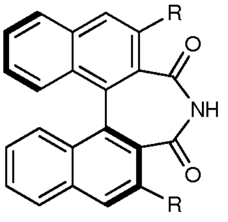


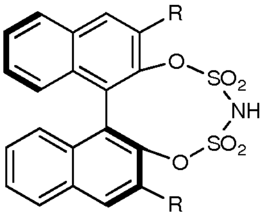












In said formulae, R can have the meaning as given above for R in formula (IV) and its preferred embodiments.

The inventive process is usually carried out in conventional organic solvent such as hydrocarbon solvents such as hexanes, pentane, methylcyclohexane, heptane, isooctane preferably cyclohexane, halogenated solvents such as chloroform, dichloromethane, dichloroethane, chlorobenzene, fluorobenzene, preferably carbon tetrachloride, aromatic solvents such as benzene, toluene, substituted benzenes, xylenes, ethers such as tetrahydrofuran, methyltetrahydrofuran, tert-butylmethyl ether, diisopropyl ether, diethyl ether, dioxane, esters such as ethyl acetate, isopropyl acetate, or any other solvent or mixtures thereof that do not negatively influence the reaction,

The inventive process can be carried out under an atmosphere of gas that does not negatively influence the reaction, preferably in a protective atmosphere such as nitrogen, argon, or in air, preferably in a closed container.

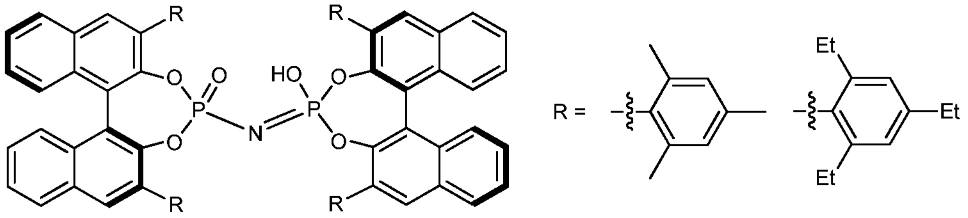
The process temperature is usually from –78 °C to 100 °C, preferably -20 to 25 °C. Addition of a drying agent such as $MgSO_4$, Na_2SO_4, or molecular sieves to the reaction mixture to partially remove water, is not necessary but can have beneficial effect on the reaction rate, enabling lower catalyst loadings, reduced reaction time, and possibly increase in enantioselectivity.

Though each peroxide might be generally used for the inventive oxidation method, the reaction conditions might be optimized by the choice of the peroxide compound, in particular with respect to the reaction rate and enantioselectivity.

The invention is further illustrated by the following Examples.

<u>Experimental Part</u>

In the following Examples, the general method for oxidizing thiocompounds using hydrogen peroxide is carried out in an organic solvent such as hexane or CCl_4 in the presence of an exemplary catalyst such as imidodiphosphate catalyst as exemplified for compounds 5a and 5b. The catalyst preparation is carried out in line with the procedure as illustrated in EP12150663.8 in detail.



5a **5b**

With the addition of $MgSO_4$ to remove water, the reaction time can be significantly shortened to 2 hours, and only 1.05 equivalents of hydrogen peroxides are required (entry 3). Both cyclohexane and CCl_4 can be employed as the solvent, giving the same results (entries 3-4). Moreover, the catalyst loading can be lowered to 1 mol%, without erosion of enantioselectivity, though needing a longer reaction time (entry 5). Further lowering the catalyst loading to 0.1 mol% can also give a high enantioselectivity of 95:5 er (entry 6).

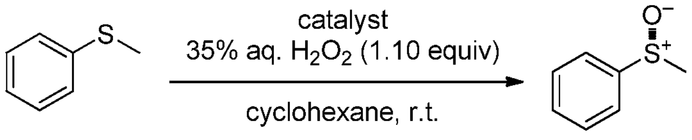


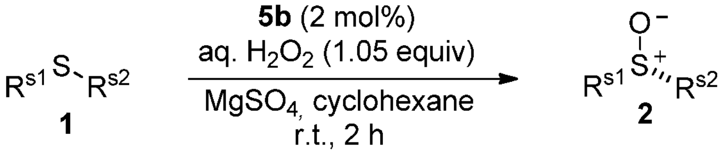
Table - Test of bisphosphonimide catalysts. [a]

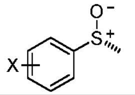
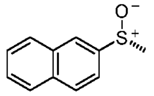
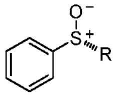
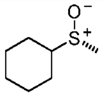
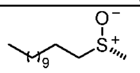
Entry	Acid	t (h)	Conversion (%)[b]	Sulfonyl compound (%)[b]	e.r.[c]
1	**5a**	24	90	n.d.	92:8
2	**5b**	24	80	n.d.	99:1
3[d]	**5b**	2	>99	n.d.	99:1
4[d,e]	**5b**	2	>99	n.d.	99:1
5[d,f]	**5b**	10	>99	n.d.	98.5:1.5
6[d,g]	**5b**	72	75%	n.d.	95:5

[a] 0.1 mmol scale, 2 mol% acid, aq. H_2O_2 (1.10 eq), in cyclohexane (2 mL), r.t.
[b] Determined by GCMS, n.d. = not detected.
[c] Determined by chiral HPLC analysis.
[d] With $MgSO_4$, aq. H_2O_2 (1.05 eq).
[e] In CCl_4.
[f] 1 mol% catalyst.
[g] 0.1 mol% catalyst.

As it can be seen from the above table, a perfect enantioselectivity was observed with acid **5b**. Having the optimized reaction conditions established, the inventors next examined the reaction scope with a series of representative substrates. As revealed in following Table, a remarkable broad range of aryl methyl sulfides can be converted to the corresponding sulfoxides in high yields with excellent enantio- and chemoselectivity, regardless the electronic nature (from –OMe to –NO_2) and position (*o*–, *m*–, *p*–) of the substituents. Substrates with a bulky alkyl group can also be oxidized with high enantioselectivity, yet a small amount of sulfone (5-9%) was observed. Remarkably, high yields and optical purity were also obtained in the cases of simple alkyl thioethers. To the best of the inventor´s knowledge, the levels of enantioselectivity are the highest so far in organocatalytic systems, and the generality of this novel organocatalytic sulfoxidation is also unprecedented,[8] even when compared to the metal-catalyzed reactions.

Table - Substrate scope of asymmetric sulfoxidation.



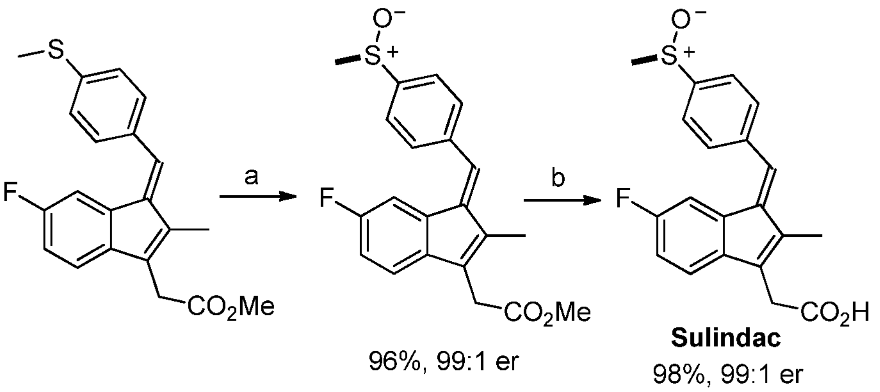
Entry	Product (R^{s1} and R^{s2} as generally defined above and being identifiable from below)	Yield(%)[a]	e.r.[b]
			
1	X = H (**2a**)	98%	99.5:0.5
2	4-MeO (**2b**)	96%	97.5:2.5
3	4-Me (**2c**)	98%	98:2
4	4-Cl (**2d**)	91%	98.5:1.5
5	3-Cl (**2e**)	95%	99.5:0.5
6	2-Cl (**2f**)	99%	99:1
7	4-CN (**2g**)	92%	97.5:2.5
8	4-NO_2 (**2h**)	95%	99.5:0.5
9	 (**2i**)	98%	99:1
			
10[d]	R = Et (**2j**)	90%	95:5
11[e]	*i*-Pr (**2k**)	89%	92.5:7.5
12[f]	 (**2l**)	96%	97:3
13[f,g]	 (**2m**)	96%	95.5:4.5

[a] Isolated yields on 0.1-0.4 mmol scales.
[b] Determined by HPLC analysis on a chiral phase.
[d] 5% sulfone observed by ^{1}H NMR.
[e] 9% sulfone.
[f] In CCl_4, at 0 °C.
[g] 2% sulfone.

The practical synthetic relevance of the inventive method was demonstrated with the enantioselective synthesis of Sulindac, which is an efficient non-steroidal anti-inflammatory drug and recently applied also to the cancer treatment. The oxidation of the

Sulindac sulfide was performed under standard reaction conditions, followed by the hydrolysis of the ester group, giving Sulindac in 98% yield and 99:1 er.

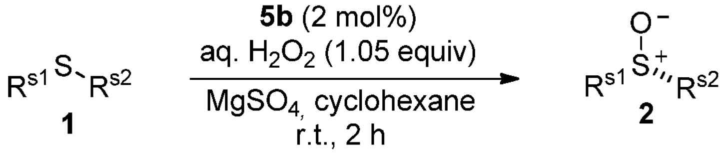
Scheme - Enantioselective synthesis of Sulindac.



(a) 2 mol% **5b**, aq. H_2O_2, $MgSO_4$, CCl_4; (b) LiOH, THF/H_2O 5:1

In summary, a novel and highly efficient organocatalytic oxidation system, chiral Brønsted acid/aq. H_2O_2, has been developed, and successfully applied to the sulfoxidation of thioethers with excellent enantioselectivity and chemoselectivity. The observed generality and high levels of enantioselectivity are unprecedented in the area of organocatalytic sulfoxidation reactions.

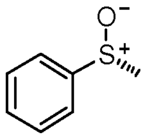
General Procedure for the Asymmetric Oxidation of Sulfides in the presence of a imidodiphosphate catalyst



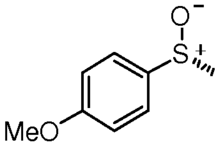
To a solution of phenyl methyl sulfide (24 mg, 24 µL, 0.2 mmol, 1.0 equiv) and the acid catalyst **5b** (6 mg, 4.0 µmol, 0.02 equiv) in 2 mL of cyclohexane was added $MgSO_4$ (90 mg) and aq. H_2O_2 (35%, 18 µL, 0.21 mmol, 1.05 equiv) in one portion. The resulting mixture was stirred vigorously at room temperature until no more conversion was observed by TLC or GCMS (2 h). Purification by column chromatography on silica gel (EtOAc) gave the desired sulfoxide as a white solid. The ratios of sulfoxide/sulfone were determined by ^{1}H-NMR analysis of the crude product. The optical purity of the product was determined by HPLC analysis (Daicel Chiralcel OB-H, heptane/isopropanol 70:30, 0.5

ml/min, 254 nm). The absolute configuration of the sulfoxide was determined by comparison of the HPLC retention times and the optical rotation with the literature values.

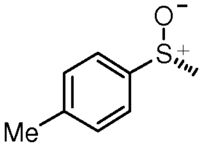
The following compounds were produced in line with the general procedure as detailed before:



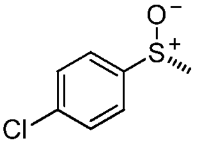
C_7H_8OS (140.20 g/mol), white solid, purified by column chromatography on silica gel (EtOAc), 98% yield; ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 2.73 (s, 3H, C*H*$_3$), 7.50-7.55 (m, 3H, Ar*H*), 7.66 (d, *J* = 7.8 Hz, 2H, Ar*H*); ^{13}**C NMR** (75 MHz, $CDCl_3$): δ 44.0, 123.5, 129.4, 131.0, 145.7 (d); **MS** (EI): m/z 140 (M^+); **HPLC**: The optical purity (er = 99.5:0.5) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 70:30, flow rate: 0.5 mL/min, 254 nm, t_r= 13.4 and 21.8 min).



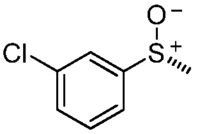
$C_8H_{10}O_2S$ (170.23 g/mol), white solid, purified by column chromatography on silica gel (EtOAc/hexanes, 1:1), 96% yield; ^{1}**H NMR** (500 MHz, $CDCl_3$): δ 2.70 (s, 3H, C*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 7.03 (dt, *J* = 8.8, 2.0 Hz, 2H, Ar*H*), 7.60 (dt, *J* = 8.8, 2.0 Hz, 2H, Ar*H*); ^{13}**C NMR** (125 MHz, $CDCl_3$): δ 44.0, 55.5, 114.8, 125.5, 136.6, 162.0; **MS** (EI): m/z 170 (M^+); **HPLC**: The optical purity (er = 97.5:2.5) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r= 11.7 and 19.0 min).



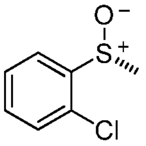
$C_8H_{10}OS$ (154.23 g/mol), white solid, purified by column chromatography on silica gel (EtOAc/hexanes, 1:1), 98% yield; ^{1}**H NMR** (500 MHz, $CDCl_3$): δ 2.41 (s, 3H, Ar-C*H*$_3$), 2.71 (s, 3H, C*H*$_3$), 7.33 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.54 (d, *J* = 8.2 Hz, 2H, Ar*H*); ^{13}**C NMR** (125 MHz, $CDCl_3$): δ 21.4, 44.0, 123.6, 130.1, 141.5, 142.5; **MS** (EI): m/z 154 (M^+); **HPLC**: The optical purity (er = 98:2) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 220 nm, t_r= 9.5 and 15.2 min).



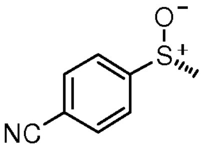
C_7H_7ClOS (174.65 g/mol); white solid, purified by column chromatography on silica gel (EtOAc), 97% yield; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.73 (s, 3H, C*H*$_3$), 7.52 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.60 (d, *J* = 8.5 Hz, 2H, Ar*H*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 44.0, 125.0, 129.7, 137.3, 144.2; **MS** (EI): m/z 174 (M^+); **HPLC**: The optical purity (er = 98.5:1.5) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r= 9.9 and 12.5 min).



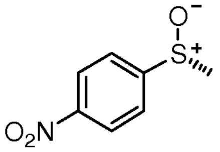
C_7H_7ClOS (174.65 g/mol); white solid, purified by column chromatography on silica gel (EtOAc), 95% yield; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.75 (s, 3H, C*H*$_3$), 7.47-7.51 (m, 3H, Ar*H*), 7.67 (d, *J* = 0.8 Hz, 1H, Ar*H*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 44.0, 121.6, 123.6, 130.6, 131.2, 135.7, 147.8; **MS** (EI): m/z 174 (M^+); **HPLC**: The optical purity (er = 99.5:0.5) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r= 10.4 and 12.7 min).



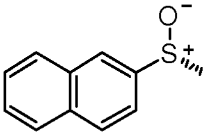
C_7H_7ClOS (174.65 g/mol); white solid, purified by column chromatography on silica gel (EtOAc/hexanes, 1:1), 99% yield; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.83 (s, 3H, C*H*$_3$), 7.40 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar*H*), 7.45 (td, *J* = 7.6, 1.4 Hz, 1H, Ar*H*), 7.55 (td, *J* = 7.5, 1.1 Hz, 1H, Ar*H*), 7.96 (dd, *J* = 7.8, 1.4 Hz, 1H, Ar*H*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 41.8, 125.3, 128.2, 129.8, 132.0, 143.7; **MS** (EI): m/z 174 (M^+); **HPLC**: The optical purity (er = 99:1) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r= 10.1 and 14.0 min).



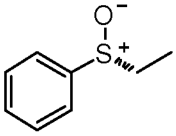
C_8H_7NOS (165.21 g/mol), white solid, purified by column chromatography on silica gel (EtOAc), 92% yield; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.77 (s, 3H, C*H*$_3$), 7.78 (dt, *J* = 8.6, 2.0 Hz, 2H, Ar*H*), 7.84 (dt, *J* = 8.6, 2.0 Hz, 2H, Ar*H*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 43.8, 114.8, 117.7, 124.3, 133.0, 151.5; **MS** (EI): m/z 165 (M^+); **HPLC**: The optical purity (er = 97.5:2.5) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r= 21.5 and 26.7 min).



$C_7H_7NO_3S$ (185.20 g/mol), white solid, purified by column chromatography on silica gel (EtOAc), 95% yield; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.80 (s, 3H, C*H*$_3$), 7.84 (dt, *J* = 8.7, 1.9 Hz, 2H, Ar*H*), 7.85 (dt, *J* = 8.7, 1.9 Hz, 2H, Ar*H*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 43.9, 124.5, 124.7, 149.5, 153.3; **MS** (EI): m/z 185 (M^+); **HPLC**: The optical purity (er = 99.5:0.5) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r= 24.7 and 28.4 min).

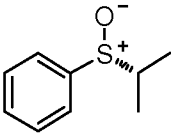


$C_{11}H_{10}OS$ (190.26 g/mol), white solid, purified by column chromatography on silica gel (EtOAc), 98% yield; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.80 (s, 3H, C*H*$_3$), 7.59-7.62 (m, 3H, Ar*H*), 7.90-8.00 (m, 3H, Ar*H*), 8.22 (d, *J* = 1.5 Hz, 1H, Ar*H*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 43.8, 119.4, 124.1, 127.4, 127.8, 128.1, 128.5, 129.6, 132.9, 134.4, 142.7; **MS** (EI): m/z 190 (M^+); **HPLC**: The optical purity (er = 99:1) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r= 11.4 and 14.0 min).

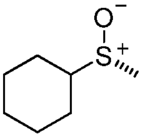


$C_8H_{10}OS$ (154.23 g/mol); white solid, purified by column chromatography on silica gel (EtOAc), 90% yield; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.19 (t, *J* = 7.4 Hz, 3H, C*H*$_3$), 2.76 (m, 1H, C*H*$_2$), 2.90 (m, 1H, C*H*$_2$), 7.47-7.54 (m, 3H, Ar*H*), 7.60-7.62 (m, 2H, Ar*H*); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 5.9, 50.2, 124.1, 129.1, 130.9, 143.3; **MS** (EI): m/z 154 (M^+); **HPLC**:

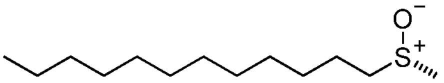
The optical purity (er = 95:5) was determined by HPLC (DAICEL OB-H, heptane/isopropanol x, flow rate: 0.5 mL/min, 254 nm, t_r= 9.4 and 14.8 min).



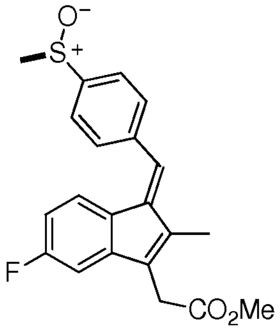
$C_9H_{12}OS$ (168.26 g/mol), colorless oil, purified by column chromatography on silica gel (EtOAc/hexanes, 1:1), 89% yield; ^{1}**H NMR** (500 MHz, $CDCl_3$): δ 1.14 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.23 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 2.84 (m, 1H, C*H*), 7.50 (m, 3H, Ar*H*), 7.60 (m, 2H, Ar*H*); ^{13}**C NMR** (125 MHz, $CDCl_3$): δ 14.0, 15.9, 54.5, 125.0, 128.9, 131.0, 141.7; **MS** (EI): m/z 168 (M^+); **HPLC**: The optical purity (er = 92.5:7.5) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r= 8.6 and 11.5 min).



$C_7H_{14}OS$ (146.25 g/mol); white solid, purified by column chromatography on silica gel (EtOAc), 96% yield; ^{1}**H NMR** (500 MHz, $CDCl_3$): δ 1.25-1.46 (m, 5H, C*H*$_2$), 1.71-1.74 (m, 1H, C*H*$_2$), 1.87-1.95 (m, 3H, C*H*$_2$), 2.14-2.17 (m, 1H, C*H*$_2$), 2.49-2.55 (m, 4H, SC*H*$_3$); ^{13}**C NMR** (125 MHz, $CDCl_3$): δ 24.9, 25.2, 25.4, 25.5, 26.0, 35.2, 60.9; **HPLC**: **MS** (EI): m/z 146 (M^+); **HPLC**: The optical purity (er = 97:3) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 90:10, flow rate: 0.5 mL/min, 220 nm, t_r= 8.6 and 11.5 min).



$C_{13}H_{28}OS$ (232.43 g/mol); white solid, purified by column chromatography on silica gel (EtOAc), 96% yield; ^{1}**H NMR** (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.26-1.35 (m, 16H, C*H*$_2$), 1.39-1.52 (m, 2H, C*H*$_2$), 1.74-1.77 (m, 2H, C*H*$_2$), 2.60 (s, 3H, SC*H*$_3$), 2.68 (m, 1H, SC*H*$_2$), 2.78 (m, 1H, SC*H*$_2$); ^{13}**C NMR** (125 MHz, $CDCl_3$): δ 14.1, 22.6, 22.7, 28.8, 29.19, 29.25, 29.34, 29.36, 29.5, 29.6, 31.9, 38.2, 54.6; **MS** (EI): m/z 232 (M^+); **HPLC**: The optical purity (er = 95.5:4.5) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 98:2, flow rate: 0.5 mL/min, 220 nm, t_r= 20.4 and 22.7 min).

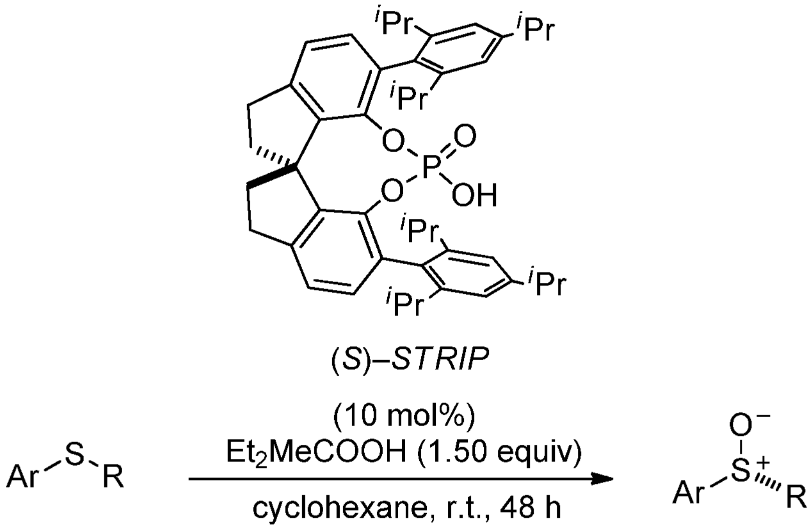


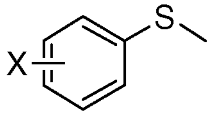
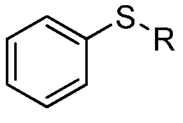
Sulindac methyl ester, $C_{21}H_{19}FO_3S$ (370.44 g/mol); white solid, purified by column chromatography on silica gel (EtOAc), 96% yield; ^{1}**H NMR** (500 MHz, $CDCl_3$): δ 2.13 (s, 3H, C*H*$_3$), 2.73 (s, 3H, C*H*$_3$), 3.49 (s, 2H, C*H*$_2$), 3.63 (s, 3H, C*H*$_3$), 6.48 (dt, *J* = 8.5 and 2.0 Hz, 1H, *CH*), 6.80 (dd, *J* = 8.5 and 2.0 Hz, 1H, *CH*), 7.06-7.08 (m, 2H, *CH*), 7.59 (d, *J* = 8.0 Hz, 2H, *CH*), 7.64 (d, *J* = 8.0 Hz, 2H, *CH*); ^{13}**C NMR** (125 MHz, $CDCl_3$): δ 10.4, 31.5, 43.8, 52.2, 106.1, 110.7, 123.6, 123.7, 128.1, 129.4, 130.2, 131.7, 138.1, 139.6, 141.5, 145.4, 146.6, 162.3, 164.2, 170.6; **MS** (EI): m/z 370 (M); **HPLC**: The optical purity (er = 99:1) was determined by HPLC (DAICEL AD-3, heptane/isopropanol 90:10, flow rate: 1 mL/min, 254 nm, t_r= 13.1 and 14.2 min).

Asymmetric Oxidation of Sulfides in the presence of a phosphate catalyst

In the following Examples, the inventors describe the use of chiral phosphoric acids, such as (*S*)-STRIP as catalysts using alkyl hydroperoxides. The inventors have found that the size of the alkyl group on the hydroperoxide oxidant had a positive effect on the enantioselectivity. For substrate in entry 1 in Table below *tert*-butyl hydroperoxide gave e.r. 87:13, and hydrogen peroxide 58:42.

Table. Substrate scope of phosphoric acid catalyzed asymmetric sulfoxidation.

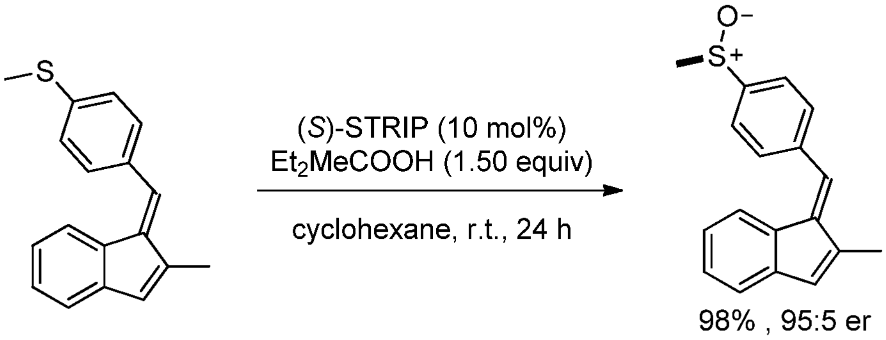


Entry	Sulfide	Yield	e.r.
			
1	X = H	93%	91:9
2	4-MeO		93:7
3	4-Me	92%	94:6
4	4-Cl	88%	93:7
5	3-Cl	88%	93:7
6	2-Cl	88%	90:10
7	4-NO_2	95%	90:10
			
8	R= *i*-Pr	92%	93:7
9	*R*= *t*-Bu	88%	95:5

Reaction scope was investigated under the optimized reaction conditions. As shown in the Table above, the substrate scope is quite general, various sulfides, electron-rich or poor can all be converted into desired sulfoxides in high chemical yields and high enantioselectivities. Remarkably, bulky groups are also tolerated quite well, and even higher enantioselectivity was observed with substrates like pheny tertbutyl sulfide (entry

9). To the best of inventors knowledge, 95:5 er is the best results so far and even enzymes failed to oxidize this difficult substrate with high enantioselectivity.

A synthetic application of this novel organocatalytic method was carried out in the preparation of a Sulindac analogue. Under optimized conditions, sulfide **3** was converted into sulfoxide **4** in 98% yield and 95:5 er.



3

4

Scheme 3. Synthesis of a potent inhibitor of histone deacetylases.

Claims

1. Process for the asymmetric oxidation of a nucleophilic organic compound by electrophilic addition of a peroxide compound, wherein the organic compound is reacted with a peroxide compound R^p-OOH in the presence of a chiral acid catalyst, said chiral acid catalyst being selected from the group of chiral acids consisting of chiral imidodiphosphates, phosphoric acids, sulfonic acids, carboxylic acids, bisulfonimides, triflyl phosphoramides, phosphinyl phosphoramides and derivatives thereof, said chiral acid catalyst comprising a catalytically active site [-(P,S,C)=O][(-NHR^E,-OH] – wherein R^E has the meaning of an electron-withdrawing group, and ,

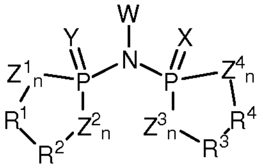
2. The process of claim 1 wherein the organic compound to be oxidized is selected from $X^sR^X{}_n$, $R^{s1}R^{s2}C{=}CHR^{s3}R^{s4}$ and $R^{s1}R^{s2}CH\text{-}(C{=}O)R^{s3}$, wherein
   - X^s can be selected from S, Se, P or N,
   - R^X can be the same or different on X and may be selected from $-NR^Y{}_2$, $-SR^Y$, $-OR^Y$, $-OSiR^y{}_3$, C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, each hydrocarbon optionally being substituted by one or more groups selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl or heterosubstituents,
   - n is 2 when X^s is S or Se, and n is 3 when X^s is P or N,
   - R^p, R^Y and R^{s1} to R^{s4} may be independently selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, each hydrocarbon optionally being substituted by one or more groups selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially

arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl or heterosubstituents.

3. A process according to any of claims 1 to 2, wherein the organic compound is a thioether R^{s1}-S-R^{s2} wherein R^{s1} and R^{s2} have the meaning as given in claim 2.

4. The process according to any of claims 1 to 3, wherein the peroxide R^p-OOH is selected from hydrogen peroxide, aliphatic or aromatic hydroperoxide, aliphatic or aromatic percarboxylic acid having a C_1 to C_{20} straight chain, branched chain or cyclic aliphatic or C_6 to C_{20} aromatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, each hydrocarbon optionally being substituted, or mixtures thereof.

5. The process according to any of claims 1 to 4 wherein said imidodiphosphate catalyst is having the general formula (I)



(I)

wherein:

X and Y may be, independently from each other, the same or different and represent O, S, Se and NR^N,

Z^1 to Z^4 may be, independently from each other, the same or different and represent O, S and NR^N,

n stands for 0 or 1,

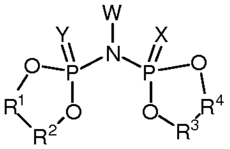
W may be substituent being capable of forming a covalent or ionic bond with the imidodiphosphate moiety,

R^1 to R^4 may be, independently from each other, the same or different and may be each an aliphatic, heteroaliphatic, aromatic or heteroaromatic group, each optionally being further substituted by one or more heterosubstituents, aliphatic, heteroaliphatic, aromatic or heteroaromatic groups whereby R^1 and R^2 are forming a ring system with Z^1 and Z^2 and R^3 and R^4 are forming a ring system with Z^3 and Z^4, respectively, and

R^N may be selected from hydrogen, C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, each hydrocarbon optionally being substituted by one or more groups selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl or heterosubstituents,

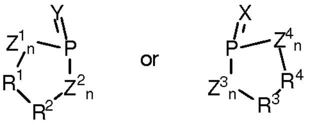
including its tautomeric and ionic forms, and derivatives thereof,

6. A process according to claim 5, wherein a chiral imidodiphosphate is used, wherein in formula (I), Z^1 to Z^4 represent O, n is 1, R^1 to R^4, R, X and Y as well as W are as defined before, as represented by formula (II):



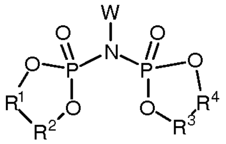
(II)

7. A process according to claim 5 or 6, wherein a chiral imidodiphosphate is used, wherein at least one moiety



is a five to ten-membered ring structure and R^1 to R^4, R, X and Y as well as W are as defined before.

8. A process according to claim 5 to 7, wherein a chiral imidodiphosphate is used, wherein in formula (I), Z^1 to Z^4 represent O, n is 1, X and Y represent O, R^1 to R^4 as well as W are as defined before, as represented by formula (III):



(III)

9. A process according to claim 8, wherein, in such formula (III),
   - R^1 to R^4, respectively may each be selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, each hydrocarbon optionally being substituted by one or more groups selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl or heterosubstituents, and
   - W may be selected from hydrogen, -OH, halogen, a metal such as Li, Na, K, Rb, Cs, Be, Mg, Ca, Sr, Ba Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Y, Zr, Mo, Ru, Rh, Pd, Ag, W, Re, Os, Ir, Pt, Au, Al, Pb, La, Sm, Eu, Yb, U, or a cationic organic group, R^w or a substituted silicon –$SiR^IR^{II}R^{III}$, wherein R^w, R^I, R^{II} and R^{III} may be same or different and each stand for hydrogen, halogen, C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, each hydrocarbon optionally being substituted by one or more groups selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms thereof, such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, or heterosubstituents,

   including its tautomeric and ionic forms, and derivatives thereof.

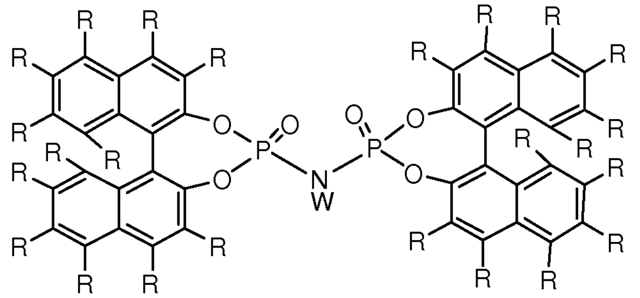
10. A process according to claim 8 or 9, wherein, in such formula (III), (R^1 and R^2) and (R^3 and R^4), respectively each form a ring structure which may be the same or different and is derived from a bridged, optionally dimeric, aromatic structure such as biphenyl optionally substituted, BINOL, TADDOL, VAPOL, SPINOL, 1,1′-binaphthalene, 1,1′-bianthracene, 1,1-biphenanthrene, or a partially arene-hydrogenated form of such aromatic ring structure such as 8H-BINOL, each of said rings systems optionally being substituted by one or more substituents which may be the same or different on each position and may each be selected from hydrogen, heterosubstituents, C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one

or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, each hydrocarbon optionally being substituted by one or more groups selected from C_1 to C_{20} straight chain, branched chain or cyclic aliphatic hydrocarbons, optionally having one or more unsaturated bonds such as C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl or C_2-C_{20}-alkinyl, C_3-C_8-heterocycloalkyl or C_6 to C_{20} aromatic hydrocarbon and partially arene-hydrogenated forms such as aryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl or a heterosubstituent, and

W is as defined before,

including its tautomeric and ionic forms, and derivatives thereof.

11. A process according to claim 5, wherein the compound of formula (I) may be represented by formula (IV):



(IV)

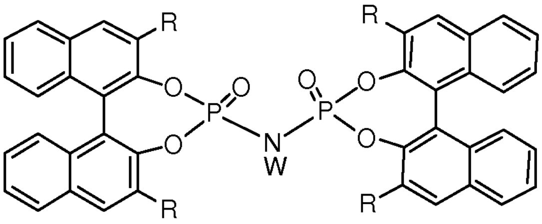
wherein in said formula (IV), the substituent R may be same or different on each position and may be heterosubstituent or R^N as defined in claim 1, and

W has the meaning as defined in claim 5.

12. A process according to any of claims 5 to 11, wherein at least one of said ring structures formed by (R^1 and R^2) or (R^3 and R^4) is chiral, preferably with a C_2 symmetry axis.

13. A process according to any of claims 5 to 11, wherein the ring structures formed by (R^1 and R^2) or (R^3 and R^4), respectively, are identical.

14. A process according to claim 5, wherein a chiral imidodiphosphate is used, represented by the following formula (IVa):



(IVa)

wherein the substituent R may be different or preferably the same on each position and may be defined as in claim 7,
W is as defined in claim 5,
including its tautomeric and ionic forms, and derivatives thereof.

15. A process according to any of claims 5 to 14, wherein the organic compound is enantioselectively oxidized with a peroxide compound in the presence of a chiral imidodiphosphate catalyst, said imidodiphosphate having the general formula (I) defined above.

16. A process according to any of claims 5 to 15 wherein, in the above formula, W has the meaning of hydrogen.