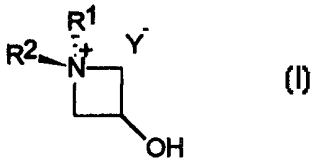
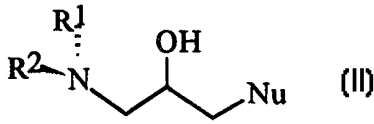




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(21) International Application Number: PCT/US99/31253 (22) International Filing Date: 30 December 1999 (30.12.99) (30) Priority Data: 60/114,363 30 December 1998 (30.12.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/114,363 (CON) Filed on 30 December 1998 (30.12.98) (71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): GODFREY, Alexander, G. [US/US]; 295 Innisbrooke Avenue, Greenwood, IN 46142 (US). PEDERSEN, Steve, W. [US/US]; 3724 Ontario Circle, Indianapolis, IN 46268 (US). DRESSMAN, Bruce, A. [-/US]; 1430 N. New Jersey, Indianapolis, IN 46202 (US).		(74) Agent: MRKSICH, K., Shannon; Brinks Hofer Gilson & Lione, P.O. Box 10087, Chicago, IL 60610 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: STEREOSPECIFIC RING OPENING OF CHIRAL AZETIDINIUM SALTS (57) Abstract <p>The invention is directed to a process for stereoselective chemical synthesis which comprises reacting a nucleophilic agent and a chiral quaternary azetidinium salt (QAS) substrate of formula (I), to produce a compound of formula (II).</p> <div style="text-align: right; margin-right: 100px;">  <p style="text-align: right;">(I)</p> </div> <div style="text-align: right; margin-right: 100px;">  <p style="text-align: right;">(II)</p> </div>		

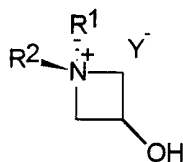
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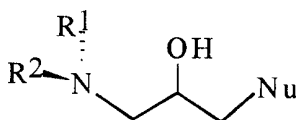
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NOVEL CHIRAL QUATERNARY AZETIDINIUM SALTS

The present invention is directed to a process of stereoselective chemical synthesis which comprises reacting a nucleophilic agent and a chiral quaternary azetidinium salt (QAS) substrate of the formula (I):



5 to produce enantiomerically enriched compounds of the formula (II):

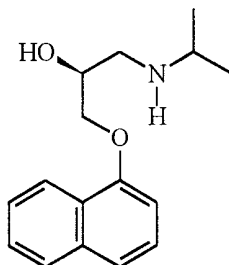


Compounds (II) possess significant biological activity.

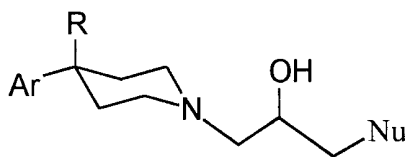
10 Biological systems are exquisitely selective and often discriminate between molecules with subtle stereochemical differences. Stereoisomers, or more specifically enantiomers, often display remarkably different biological properties (Caldwell, J. J. *Clin. Pharmacol.* **1992**, 32, 925-9; Waldeck, B. *Chirality* **1993**, 5, 350-5; Eichelbaum, M. *Dev. Pharmacol. Ther.* **1992**, 18, 131-4; Fassihi, A. R. *Int. J. Pharm.* **1993**, 92, 1-14).

15 A notorious example of this difference of biological activities between enantiomers was exemplified by thalidomide which was widely used in the early 1960's as a racemate in the prevention of miscarriages until it was removed from the market upon discovery of its teratogenic properties (Barreiro, E. J.; Ferreira, V. F.; Costa, P. R. R. *Quim. Nova* **1997**, 20, 647-656). Later studies in rats demonstrated that only the S-(-) antipode (enantiomer) was teratogenic (Blaschke, G.; Kraft, H. P.,
20 Fickentscher, K.; Koehler, F. *Arzneim.-Forsch.* **1979**, 29, 1640-2). Another example where biological effects differ greatly is the well known beta-blocker, propranolol,

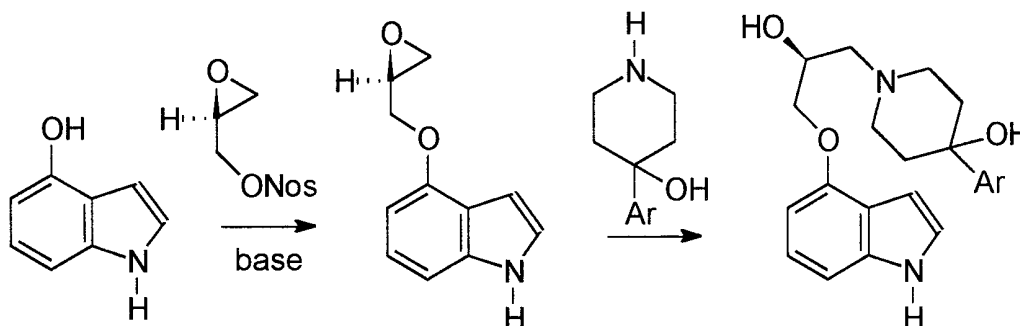
where the S-(-)-isomer is nearly two orders of magnitude more active than its enantiomer (Barrett, A. M.; Cullum, V. A. *Brit. J. Pharmacol.* **1968**, 34, 43-55).



One class of compounds which has been demonstrated to have biological activity has the formula:



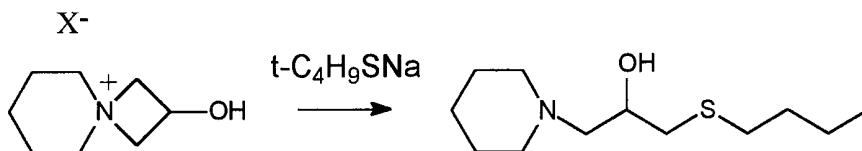
These compounds are currently generated using an epoxide intermediate as shown in the following process:



Unfortunately, the necessary epoxide intermediates are often highly mutagenic or carcinogenic. Further, some aromatic alcohol derivatives are incompatible with the epoxide reagent or render the intermediate molecule unstable. Accordingly, novel methods for enantioselectively synthesizing these compounds are desired.

Ring-opening alkylations of 1,1-dialkyl-3-substituted azetidinium cations have been investigated by V.R. Gaertner in "Ring-Opening Alkylations Of 1,1-Dialkyl-3-Substituted Azetidinium Cations, Substituent Entropy-Controlled Strained Ring-Chain

Equilibria," *J. Org. Chem.* 33:523-530 (February, 1968). Gaertner states that the alkylation reaction of the crystalline salt of piperidine can be performed as follows:

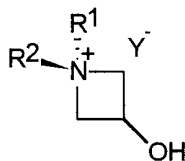


Gaertner did not address whether the reaction can be performed enantioselectively.

5 Therefore, there remains a need for a process that facilitates stereoselective formation of compounds containing an amino alcohol functionality.

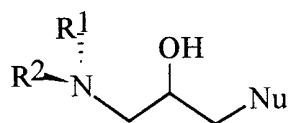
SUMMARY OF THE INVENTION

10 One aspect of the present invention is a process for stereoselective chemical synthesis which comprises reacting a nucleophilic agent and a chiral quaternary azetidinium salt (QAS) substrate of the formula (I):



15 where Y is a counterion and where either R¹ and R² are different and are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, and 5-10 membered heterocyclic group containing at least one N, S or O; or wherein R¹ and R², together with the N which they substitute, form a 5-8 membered ring system containing 0, 1, 2, or 3 heteroatoms selected from NR³R⁴, O or S; and wherein each of R¹ and R² may be unsubstituted or substituted one to three times with a substituent selected from the group consisting alkyl, alkenyls, alkynyls, halogen, 20 hydroxy, oxo, phosphoryl, thiol, sulfinyl, sulfonyl, aryl, 5-10 membered heterocyclic group containing at least one N, S or O, amine, imine, nitro, cyano, amidino, carbonyl; wherein the moieties substituted on the hydrocarbon chain can themselves be substituted with one to three further substituents;

in solution for a time sufficient to produce a compound of the formula (II)

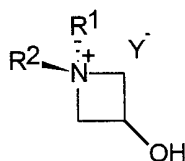


where R^1 and R^2 are defined as above, and

Nu is a negative ion or a molecule that has an unshared pair of electrons.

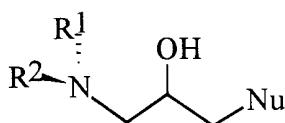
Another aspect of the present invention is a chiral quaternary azetidinium salt

5 (QAS) substrate of the formula (I):



where either Y, R^1 and R^2 are defined as above.

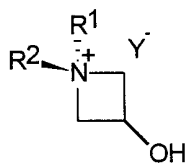
Yet another aspect of the invention is an enantiomerically enriched compound
of the formula (II)



10

where either R^1 , R^2 and Nu are defined as above.

Still another aspect of the invention is a vessel in which at least two chiral
quaternary azetidinium salts (QAS) are physically separated from each other, wherein
the QAS are of the formula (I):



15

where either Y, R^1 and R^2 are defined as above.

Still yet another aspect of the invention is directed to an assay kit for the
identification of compounds having biological or other activity, this kit comprising

assay materials and well plate apparatus where each well in this apparatus contains a compound of the library described above.

BRIEF DESCRIPTION OF THE FIGURE

5 Figure 1 shows examples of quaternary azetidinium salts useful in the process of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. Definitions

10 “Alkyl” refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone, and more preferably 20 or fewer. Likewise, preferred cycloalkyls have from 3-10
15 carbon atoms in their ring structure, and more preferably have 3-6 carbons in the ring structure. Particularly preferred alkyl groups include methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, iso-butyl, tert-butyl, sec-butyl, cyclobutyl, pentyl, hexyl, cyclohexyl, etc. Unless the number of carbons is otherwise specified, “lower alkyl” as used herein means an alkyl group, as defined above, but having from one to ten carbons, more
20 preferably from one to six carbon atoms in its backbone structure.

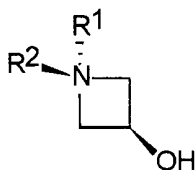
 “Alkenyl” and “alkynyl” refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one double or triple bond, respectively.

25 “Amino” means -NH_2 ; “nitro” means -NO_2 ; “halogen” designates -F , -Cl , -Br or -I ; “thiol” means -SH ; “hydroxyl” means -OH ; “sulfonyl” means =SO_2 , “sulfinyl” or “thionyl” means =SO ; and “phosphoryl” means =PO .

 “Aryl” as used herein includes 4-10 membered single-ring or fused-rings aromatic group which may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole,

pyridine, pyrazine, pyridazine, pyrimidine, naphthyl, benzothiazoline, benzothiaphene, benzofurans, indole, quinoline, etc. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycle". The aryl group can be substituted at one or more positions with such substituents as described above.

"Chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while "achiral" refers to molecules which are superimposable on their mirror image partner. In the present invention, chirality occurs due to the plane of symmetry defined by the four carbon atoms in the azetidinium ring. The hydroxy group on the ring is either above or below the plane of symmetry in relation to the substituents R^1 and R^2 as shown below:



"Electrophilic atom", "electrophilic center" and "reactive center" refer to the atom of the substrate which is attacked by, and forms a new bond to, the nucleophile.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another. "Stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Enantiomerically Enriched" refers to a product that contains a greater proportion of one particular enantiomer compared to the amount of that enantiomer in a racemic product. An enantioselective reaction yields a product with an enantiomeric excess, e.e., greater than zero. Preferred enantioselective reactions yield a product with an e.e. greater than 20%, more preferably greater than 50%, more preferably

greater than 70%, more preferably greater than 80% and most preferably greater than 90%.

An "enantioselective process" is one which favors production of one of the two possible enantiomers of a reaction product. The subject method is said to produce a
5 enantioselectively-enriched product when the yield of a particular enantiomer of the product is greater by a statistically significant amount relative to the yield of the other enantiomer. For example, when a chiral QAS is used in the ring opening reaction, the enantiomeric excess, e.e., of the reaction will be greater than if the reaction was performed using an achiral QAS.

10 "Heterocycle" or "heterocyclic group" refer to 4 to 10-membered ring structures, more preferably 5 to 7 membered rings, which ring structures include one to four heteroatoms selected from nitrogen, oxygen or sulfur. Heterocyclic groups include pyrrolidine, oxolane, thiolane, imidazole, oxazole, piperidine, piperazine, morpholine. The heterocyclic ring can be substituted at one or more positions with
15 such substituents as described above.

"Library" is a collection of compounds created by a combinatorial chemical process, the compounds having a common scaffold with one or more variable substituents. Libraries typically contain a large number of chemical derivatives used in screening for biological activity or other activity. In general a library will have greater
20 than 20 members, preferably the library will have at least 50 members, more preferably the library will have at least 96 members and most preferably the library will have at least 1000 members.

"Nucleophile" a negative ion or a molecule that has an unshared pair of electrons. Examples of nucleophilic agents suitable for use in the present invention
25 include alkyl and aromatic thiols; alkyl and aromatic alcohols; aromatic heterocyclic compounds that contain a nucleophilic nitrogen (example-the nitrogen atom of an indole, pyrrole, oxazole, thiazole, imidazole, pyrazole, isothiazole, 1,2,3-oxadiazole, 1,2,3-triazole, 1,3,4-thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, 1,3,5-

triazines, isoindole, 1H-indazole, benzimidazole, purine, benzthiazole, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, pteridine, carbazole, acridine, phenazine, phenothiazine, phenoxazine ring system); primary, secondary and tertiary amines (both cyclic and non cyclic); anilines; anionic carbon atoms (example-butyl lithium); salts of halides; alkyl and aromatic phosphines; primary and secondary alkyl or aromatic hydrazines; alkyl and aromatic hydroxylamines; salts of cyanide anion; ammonia and salts of ammonia; salts of hydroxide anion; and cyclic hydrazines.

“Racemic Mixture” or “Racemic Product” means a solution of equal amounts of two enantiomers.

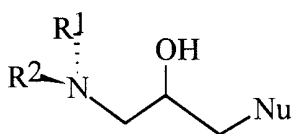
“Reaction product” means a compound which results from the reaction of a nucleophile and a substrate. In general, the term “reaction product” refers to a stable, isolatable compound, and not to unstable intermediates or transition states.

“Substrate” means a chemical compound which can react with a nucleophile according to the present invention to yield at least product having a stereogenic center.

II. Process of the present invention

II.a. General Background

In one aspect of the present invention there is provided a process for stereoselectively producing compounds of the formula (II):

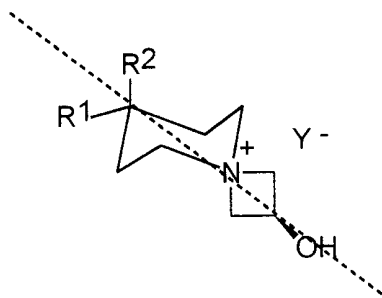


An advantage of this invention is that enantiomerically enriched products can be synthesized from chiral QAS substrates. Another advantage is that yield losses associated with the production of an undesired enantiomer can be substantially reduced.

The reactions of the present invention are enantioselective. In the present invention, a chiral QAS substrate is reacted with a nucleophile (Nu). The resulting

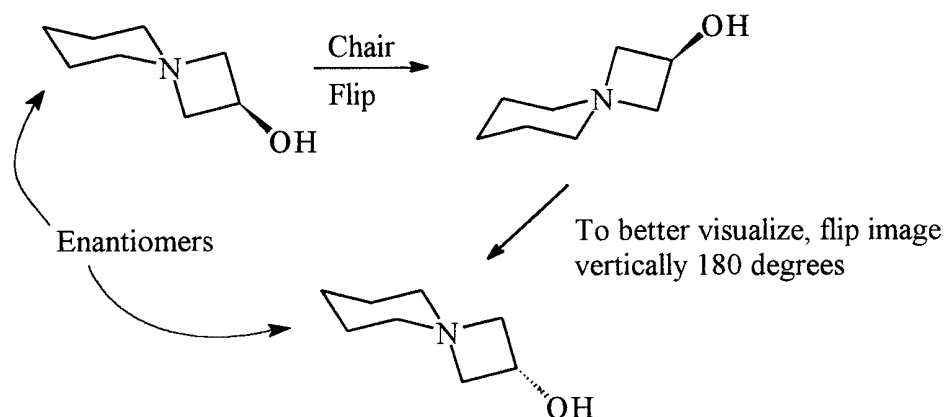
amino alcohol-containing reaction product is enantiomerically enriched and has the predetermined stereo-configuration of the chiral QAS substrate.

The QAS compounds most closely resemble the class of chiral compounds known as spiranes (Eliel, E. L.; Wilen, S. H.; Mander, L. N.; John Wiley & Sons: New York, 1994, See page 1120, Chap. 14). The chirality of chiral QAS substrates is displayed through an axis of asymmetry as displayed below:

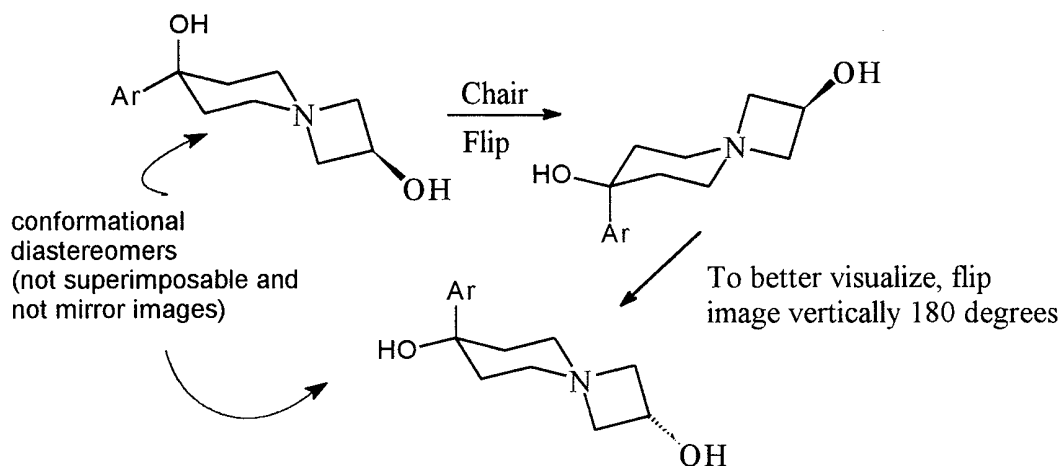


This mode of chirality is similar to the axis of symmetry which distinguishes “right-handed” helical structures from “left-handed” ones (such as used to describe DNA structures).

The identities of R¹ and R² will determine whether the chiral QAS substrate is capable of racemization through chair-flipping dynamics alone under ambient conditions. For example, if R¹ and R² were both hydrogen, distinct enantiomers of the QAS substrate would become racemic under ambient conditions due to rapid chair flipping which permits equilibration between the enantiomers, as shown in equation (3) below:



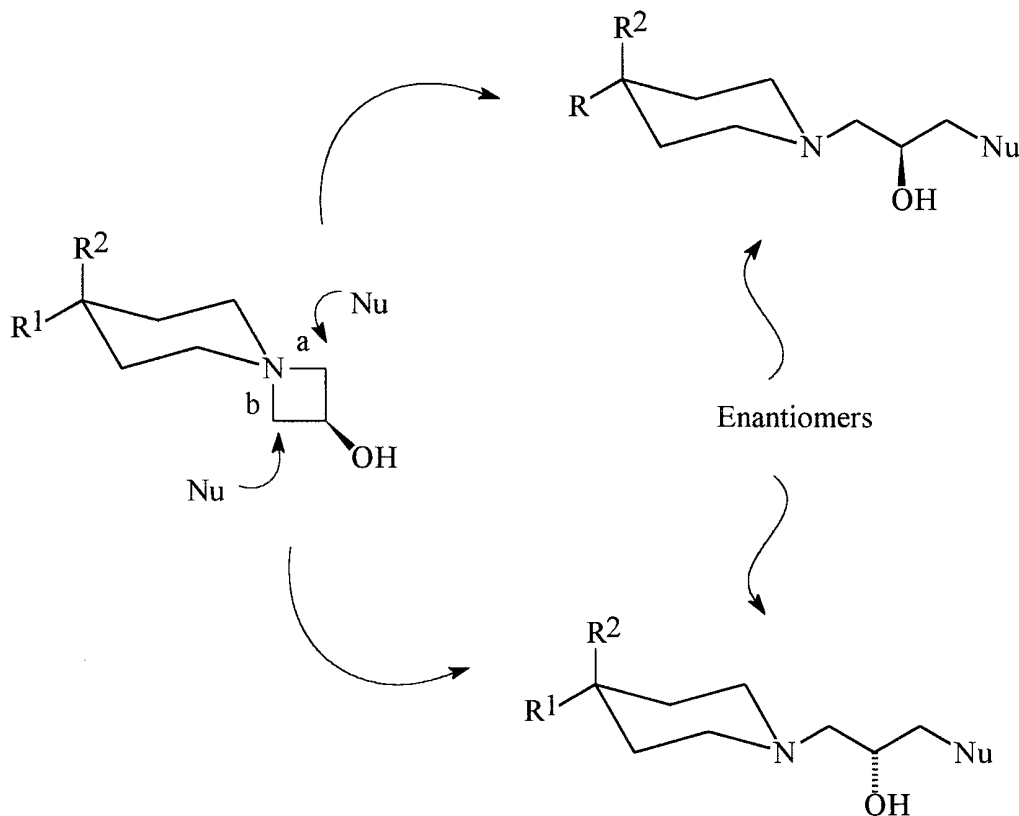
Alternatively, when R^1 and R^2 together form a 4-aromatic-4'-hydroxy piperidine ring, the chiral QAS substrate is incapable of racemization through chair flipping dynamics alone.



Plus, if R^1 and R^2 vary significantly in steric demand, sufficient rigidity can be imparted onto the molecule to hinder conformational motility. This second property is important in yielding enantio-enriched products (*vide infra*).

An indiscriminate attack by a nucleophile leading to breaking either the C-N bond (a or b; see below) of the azetidine ring would yield a racemic product. However, it is possible to achieve sufficient conformational rigidity. Differentiation of the C-N bond strengths through a combination of steric or stereoelectronic effects allows for a discriminatory attack by a nucleophile, thus yielding an enantio-enriched

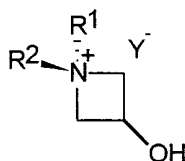
product. Thus, the chiral QAS substrates reagents can remain optically enriched, and yield a final product that is substantially enantiomerically pure.



II.b. chiral QAS substrates

5

Suitable chiral QAS compounds have the formula (I):



where R^1 and R^2 are different and are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, and 5-10 membered heterocyclic group containing at least one N, S or O;

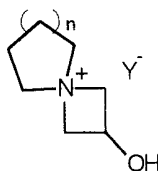
10 or wherein R^1 and R^2 , together with the N which they substitute, form a 5-8 membered ring system containing 0, 1, 2, or 3 heteroatoms selected from NR^3R^4 , O or S;

R^3 and R^4 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, aryl, and 5-10 membered heterocyclic group containing at least one N, S or O;

wherein each of R^1 , R^2 , R^3 and R^4 may be substituted one to three times with a substituent selected from the group consisting alkyl, alkenyls, alkynyls, halogen, hydroxy, oxo, phosphoryl, thiol, sulfinyl, sulfonyl, aryl, 5-10 membered heterocyclic group containing at least one N, S or O, amine, imine, nitro, cyano, amidino, carbonyl; wherein the moieties substituted on the hydrocarbon chain can themselves be substituted with one to three further substituents, if appropriate; and

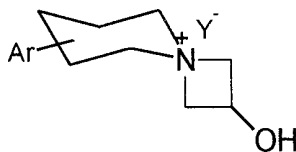
Y is an anion. Preferred anions include Cl, OH, and F.

In a preferred embodiment, the QAS (I) is a chiral spiro-azetidinium compound of the formula (III):



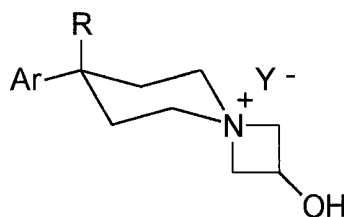
where n is 0, 1, 2, 3 or 4, preferably 1 or 2; and Y is an anion. The ring containing $-(CH_2)_n-$ can optionally be substituted with one or more substituents selected from the group consisting alkyl, alkenyls, alkynyls, halogen, hydroxy, oxo, phosphoryl, thiol, sulfinyl, sulfonyl, aryl, 5-10 membered heterocyclic group containing at least one N, S or O, amine, imine, nitro, cyano, amidino, carbonyl; wherein the moieties substituted on the hydrocarbon chain can themselves be substituted with one to three further substituents, if appropriate.

Particularly preferred chiral spiro-azetidinium compounds have the formula (IV):



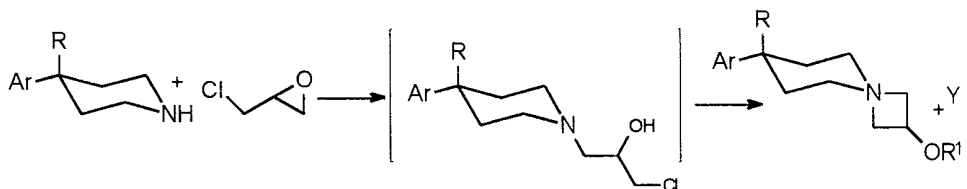
where Ar is an aryl group, Y is an anion and wherein the ring containing

-(CH₂)_n- can optionally be substituted with one or more substituents selected from the group consisting alkyl, alkenyls, alkynyls, halogen, hydroxy, oxo, phosphoryl, thiol, sulfinyl, sulfonyl, aryl, 5-10 membered heterocyclic group containing at least one N, S or O, amine, imine, nitro, cyano, amidino, carbonyl; wherein the moieties substituted on the hydrocarbon chain can themselves be substituted with one to three further substituents, if appropriate. 4-aromatic spiro-azetidinium compounds of the formula (V) are particularly preferred:



where Ar is an aromatic group (preferably naphthene, benzothiazoline, benzothiapene, and phenyl) and R is alkyl, alkenyls, alkynyls, halogen, hydroxy, oxo, phosphoryl, thiol, sulfinyl, sulfonyl, aryl, 5-10 membered heterocyclic group containing at least one N, S or O, amine, imine, nitro, cyano, amidino, carbonyl; and wherein Ar and R can be substituted with one or more, preferably with one to three further substituents, if appropriate.

Suitable chiral QAS compounds can be obtained by procedures adapted from Gaertner, Tetrahedron Letters, 343 (1967) and Gaertner, *J. Org. Chem.* 33, 523 (1968). For example, the compounds of the first embodiment can be synthesized by reacting an epichlorohydrin and a 4,4-disubstituted piperidine in methanol at reflux overnight, proceeding through the indicated amino chlorohydrin intermediate.



Thereafter, the solvent can be removed followed by the addition of a second organic solvent such as methylene chloride (CH₂Cl₂), acetonitrile, acetone, hexane or

ether, to induce precipitation and/or crystallization of the product which then can be readily isolated by filtration.

The formed chiral QAS compounds are both extremely reactive in solution yet relatively stable to handling and/or long term storage in the solid state.

5

II.c. Nucleophiles

Suitable nucleophiles (Nu) include alkyl and aromatic thiols; alkyl and aromatic alcohols; aromatic heterocyclic compounds that contain a nucleophilic nitrogen (example-the nitrogen atom of an indole, pyrrole, oxazole, thiazole, imidazole, pyrazole, isothiazole, 1,2,3-oxadiazole, 1,2,3-triazole, 1,3,4-thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, 1,3,5-triazines, isoindole, 1H-indazole, benzimidazole, purine, benzthiazole, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, pteridine, carbazole, acridine, phenazine, phenothiazine, phenoxazine ring system); primary, secondary and tertiary amines (both cyclic and non cyclic); anilines; anionic carbon atoms (example-butyl lithium); salts of halides; alkyl and aromatic phosphines; primary and secondary alkyl or aromatic hydrazines; alkyl and aromatic hydroxylamines; salts of cyanide anion; ammonia and salts of ammonia; salts of hydroxide anion; and cyclic hydrazines.

Preferred nucleophiles include aliphatic alcohols (HOR^5), aromatic alcohols (HOR^6), aliphatic thiols (HSR^7 ; also alkyl thiols or alkyl sulfides), aromatic thiols (HSR^8), and secondary amines ($\text{HNR}^9\text{R}^{10}$).

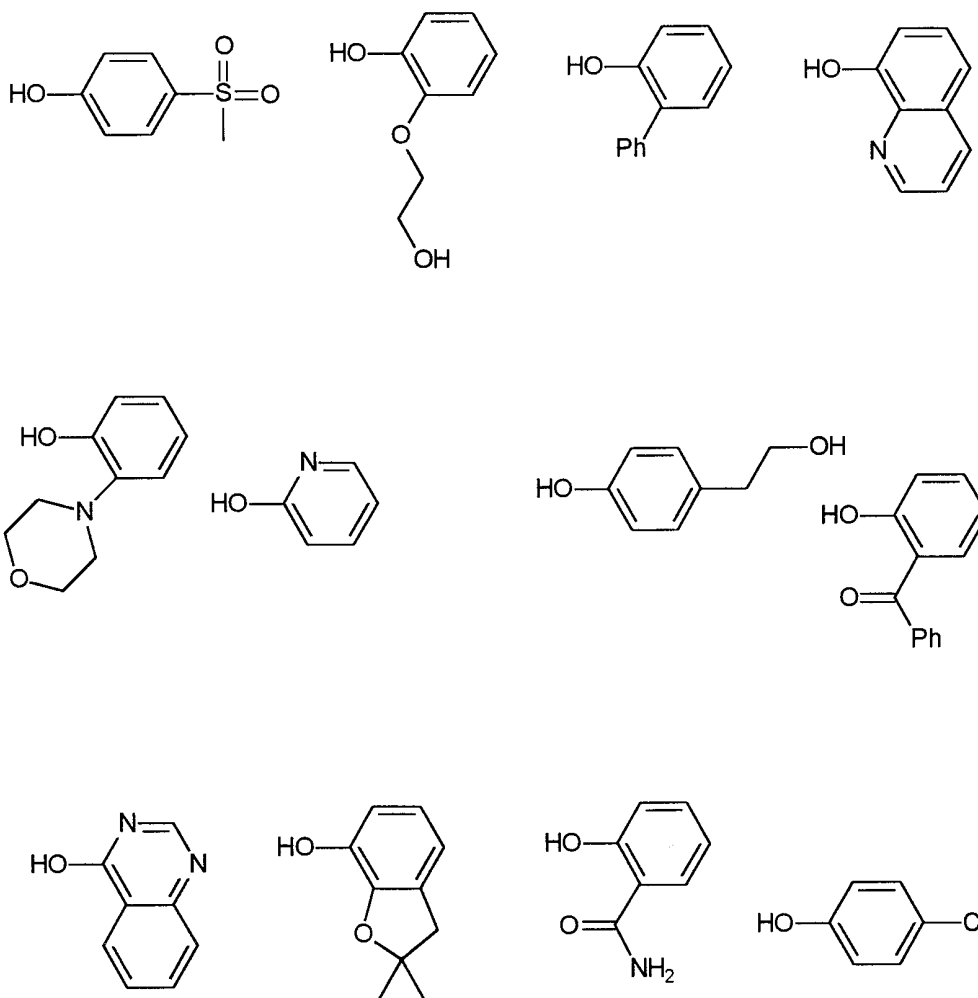
Suitable aliphatic alcohols are of the formula HOR^5 where R^5 is an alkyl group which can optionally be substituted with one or more, preferably 1-3, substituents selected from the group consisting alkyl, alkenyls, alkynyls, halogen, hydroxy, oxo, phosphoryl, thiol, sulfinyl, sulfonyl, aryl, 5-10 membered heterocyclic group containing at least one N, S or O, amine, imine, nitro, cyano, amidino, carbonyl; wherein the moieties substituted on the hydrocarbon chain can themselves be substituted with one to three further substituents, if appropriate.

Suitable aromatic alcohols are of the formula HOR^6 where R^6 is an aryl group such as phenyl, naphthyl, tetrazole, imidazole, or diazole, which can be optionally

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5 substituted with one or more, preferably 1-3, substituents selected from the group consisting alkyl, alkenyls, alkynyls, halogen, hydroxy, oxo, phosphoryl, thiol, sulfinyl, sulfonyl, aryl, 5-10 membered heterocyclic group containing at least one N, S or O, amine, imine, nitro, cyano, amidino, carbonyl; wherein the moieties substituted on the hydrocarbon chain can themselves be substituted with one to three further substituents, if appropriate.

Examples of suitable aromatic alcohols are shown below. This list is intended to demonstrate the diversity of reagents which can be used and not intended to limit the nature of the reagent in any way.

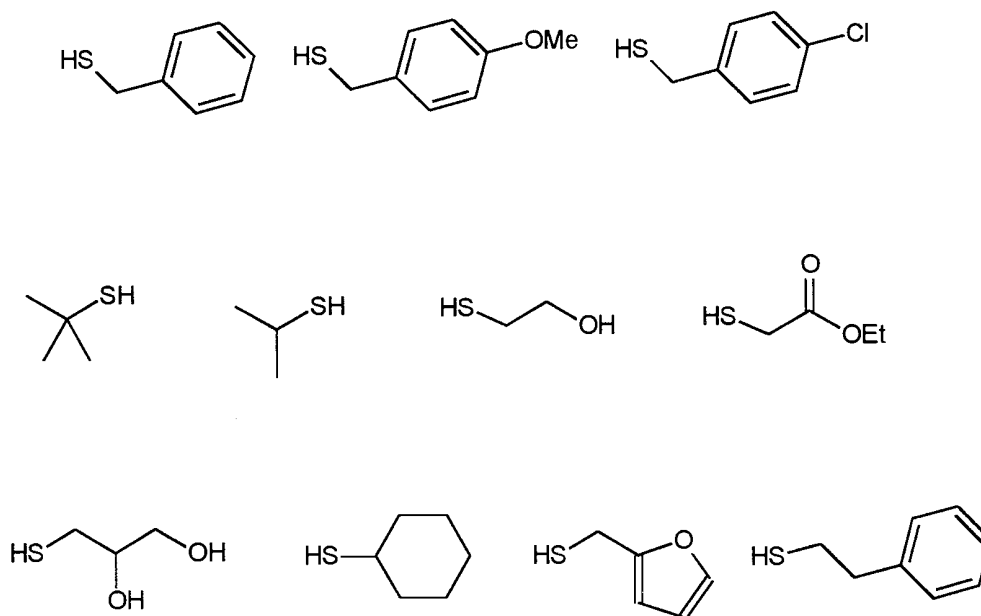


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Suitable aliphatic thiols are of the formula HSR^7 where R^7 is an alkyl group which can optionally be substituted with one or more, preferably 1-3, substituents

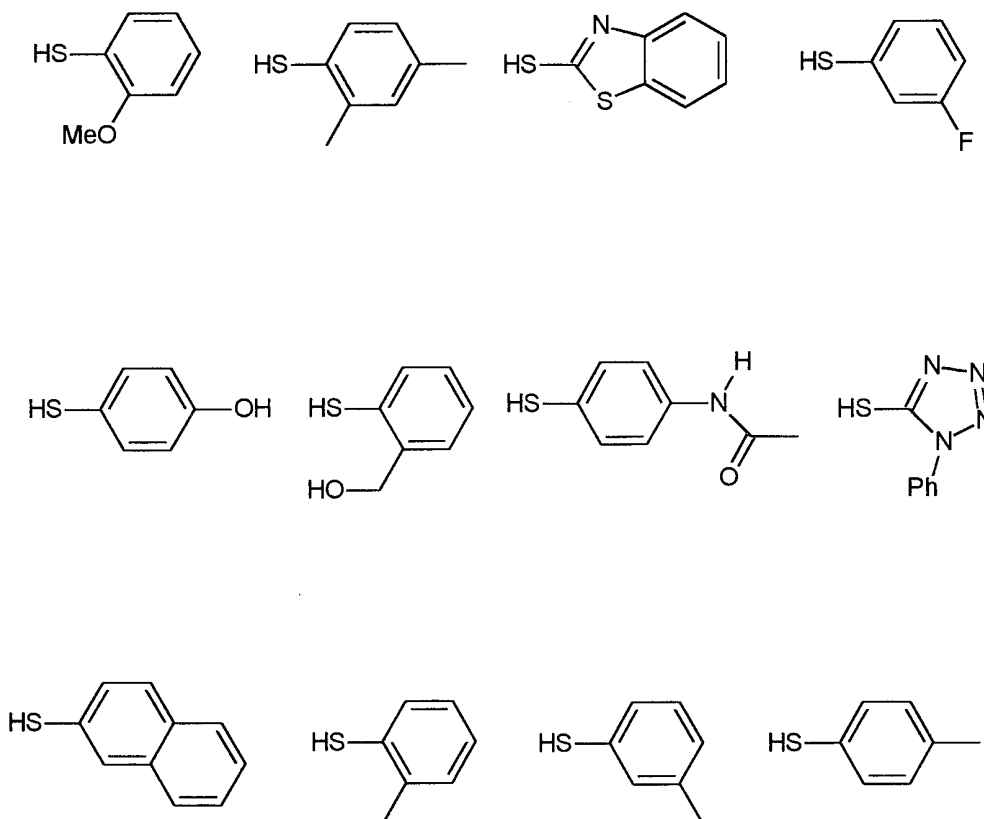
selected from the group consisting alkyl, alkenyls, alkynyls, halogen, hydroxy, oxo, phosphoryl, thiol, sulfinyl, sulfonyl, aryl, 5-10 membered heterocyclic group containing at least one N, S or O, amine, imine, nitro, cyano, amidino, carbonyl; wherein the moieties substituted on the hydrocarbon chain can themselves be substituted with one to three further substituents, if appropriate.

Examples of suitable alkyl thiols are shown below. This list is intended to demonstrate the diversity of reagents which can be used and not intended to limit the nature of the reagent in any way.



Suitable aromatic thiols are of the formula HSR⁸ where R⁸ is an aryl group such as phenyl, naphthyl, tetrazole, imidazole, or diazole, which can be optionally substituted with one or more, preferably 1-3, substituents selected from the group consisting alkyl, alkenyls, alkynyls, halogen, hydroxy, oxo, phosphoryl, thiol, sulfinyl, sulfonyl, aryl, 5-10 membered heterocyclic group containing at least one N, S or O, amine, imine, nitro, cyano, amidino, carbonyl; wherein the moieties substituted on the hydrocarbon chain can themselves be substituted with one to three further substituents, if appropriate.

Examples of suitable aromatic thiols are shown below. This list is intended to demonstrate the diversity of reagents which can be used and not intended to limit the nature of the reagent in any way.



5 Many of these compounds are commercially available. Syntheses of these classes of compounds are well described in the literature.

II.d. Process steps

10 In general the chiral QAS substrate is reacted with the nucleophile in solvent for a time and at a temperature sufficient to result in product.

Suitable solvents include any aprotic solvent, such as tetrahydrofuran (THF), dimethylformamide (DMF), dimethylsulfoxide (DMSO), dioxane, CH_2Cl_2 , toluene or acetone, or mixtures thereof. In some instances, the reaction can be conducted in mixed solvent systems which contain alcohol.

15 The reaction is conducted for at least about 1 hour, preferably overnight.

The reaction can be conducted at room temperature ($\sim 25^{\circ}\text{C}$) to the reflux point of the solvent used.

The process of the invention may be carried out in any vessel capable of holding the liquid reaction medium and having inlet and outlet means.

5 When Nu is an aliphatic alcohol, then the reaction requires the addition of a base with a $\text{pK}_a \geq 17$, such as potassium t-butoxide or n-BuLi. The reaction of a QAS and an aromatic alcohol is preferably conducted in THF, dioxane or toluene. An excess of Nu is used; that is the molar ratio of Nu:QAS is ≥ 1 and preferably is ≥ 5 . The reaction mixture is preferably refluxed overnight. The product can be purified by
10 passing the reaction mixture through a SCX column (a cation exchange resin available from Varian Sample Preparation, CA). The product adheres to the column and can be removed with either acid or base. The preferred method for removing the product is to rinse with 20% 2M NH_4^+ in methylene chloride.

15 When Nu is an alkyl thiol, the reaction is conducted in the presence of a base, preferably a resin bound base such as tetramethylammonium hydroxide (available in resin bound form from Biorad) or piperidine (which can be attached to Merrifield resin). The reaction of a QAS and an aliphatic thiol is preferably conducted in THF, dioxane or toluene. An excess of Nu is used; that is the molar ratio of Nu:QAS is ≥ 1 and preferably is ≥ 2 . The reaction mixture is preferably refluxed overnight. The
20 product can be purified by passing the reaction mixture through a SCX column (a cation exchange resin available from Varian Sample Preparation, CA). The product adheres to the column and can be removed with either acid or base. The preferred method for removing the product is to rinse with 20% 2M NH_4^+ in methylene chloride.

25 When Nu is an aromatic thiol, the reaction is conducted in the presence of a base, preferably a resin bound base such as resin bound piperidine. The reaction of a QAS and an aromatic thiol is preferably conducted in 1:1 methanol : CH_2Cl_2 . An excess of Nu is used; that is the molar ratio of Nu:QAS is ≥ 1 and preferably is ≥ 5 . The reaction mixture is preferably heated to $\sim 65^{\circ}\text{C}$ overnight. The product can be purified by passing the reaction mixture through a SCX column and washing the
30 product from the column with 20% 2M NH_4^+ in methylene chloride. Thereafter, if the

aromatic thiol contains a basic substituent, the product can be further purified by passing the material obtained off the SCX column through AG 2X hydroxide resin (an anionic resin exchange resin available from Biorad).

When Nu is an aromatic alcohol, the reaction is conducted in the presence of a base, preferably resin bound tetramethylammonium hydroxide. The reaction of a QAS and an aromatic alcohol is preferably conducted in toluene, THF or dioxane. An excess of Nu is used; that is the molar ratio of Nu:QAS is ≥ 1 and preferably is ≥ 10 . The reaction mixture is preferably heated to $\sim 65^{\circ}\text{C}$; and generally the reaction is allowed to proceed longer than when other Nu are used, preferably for at least ~ 48 hours. The product can be purified by passing the reaction mixture through a SCX column and washing the product from the column with 20% 2M NH_4^+ in methylene chloride. Thereafter, the product can be concentrated and further purified, redissolved and passed through a silica plug, preferably using a mixed solvent such as 15% MeOH: CH_2Cl_2 .

Secondary amines

When Nu is a secondary amine, the reaction does not require an additional base. The reaction of the QAS and the secondary amine is preferably conducted in an alcoholic solvent (such as MeOH), THF or dioxane. An excess of Nu is used; that is the molar ratio of Nu:QAS is ≥ 1 and preferably is ≥ 3 . The first stage is preferably conducted at $\sim 65^{\circ}\text{C}$ and is allowed to react longer than when other Nu are used, preferably for at least ~ 48 hours.

In an optional second stage, a scavenger is added to the reaction mixture to remove excess amine. Suitable scavengers include resin bound isocyanates or aldehydes. Alternatively, excess amine can be removed using conventional methods such as column chromatography.

III. Libraries of chiral QAS substrates

For small scale synthesis of multiple products, the process of the invention is preferably carried out in containers adaptable to parallel array syntheses. With parallel array synthesis individual reaction products are prepared in each of multiple reaction

zones. The reaction zones are physically separated from one another on a solid support. Examples of solid supports include wellplates, silicone, or agar. Compounds can be added to the surface of the solid support by multiple delivery apparatus, automated or robotic apparatus, any of which may be either manually or computer controlled.

A preferred embodiment of the present invention is a diverse amine alcohol compound library in the form of a plurality of wellplates, each wellplate having wells containing a separate reaction product (library compound). In such cases, the library compounds are conveniently identified by their wellplate number and "x" column and "y" wellplate row coordinates. The process of making the library of amine alcohol compounds may be conveniently carried out in a conventional wellplate apparatus. It is particularly advantageous to carry out the method of the invention in a standard wellplate apparatus such as a plastic 96 well microtiter plate.

Typically, the wellplate apparatus is in the form of a rigid or semi-rigid plate, said plate having a common surface containing openings of a plurality of vessels arranged in rows and columns. A standard form of wellplate apparatus is a rectangular plastic plate having 8 rows and 12 columns (total 96) of liquid retaining depressions on its surface. A wellplate apparatus may optionally have other elements of structure such as a top or cover (e.g., plastic or foil), a bottom in a form such as a plate or reservoir, clamping means to secure the wellplate and prevent loss of its contained compounds.

Selection of QAS - The amount of QAS introduced into each reaction zone will depend on the desired amount of each library compound that is needed for conducting biological assays, archival storage and other related needs. Typically, the desired amount of individual reaction product is from 1 microgram to 50 milligrams.

The amount of QAS in each reaction zone is represented by the symbol "(n)", where (n) represents the equivalents of QAS.

Typically, from about 8 to about 800 diverse QASs are employed to synthesize a library of compounds using the method of the invention.

Typically, combinatorial techniques have to be very robust to work well for highly diverse groups of reactants. In the diverse amine alcohol compound library

making process described herein the is the reactant used in excess. The method of the invention contemplates solution phase reactions where a stoichiometric excess of the Nu is used. The amount of Nu used to ensure an excess is defined as at least 1.1(n) and preferably a larger excess in the range of from 1.25(n) to 5(n), where the variable (n) is as previously defined. The 1.1 multiplier is used to insure at least a 10% stoichiometric excess of Nu to drive the reaction to completion, thereby removing the QAS from each reaction zone used to create the amine alcohol compound library.

The reaction zone is maintained at a temperature and for a time sufficient to permit reaction of the first and second reagents, that is, to complete consumption of the QAS and form an amount of amine alcohol compound necessary to conduct biological assays to determine the efficacy of the prepared library compounds.

The time, temperature, and pressure of the combinatorial reaction zones used for the creation of library compounds are not critical aspects of the invention. Reaction times for a single step of the reaction are generally from 0.1 seconds to 24 hours, with times of 1 second to 60 minutes being most often used. The temperature of the reaction may be any temperature between the freezing point and the boiling point of the liquid reaction medium, but is generally between -10°C and 60°C, with 10°C to 40°C being preferred and ambient temperatures (about 20°C-30°C) being most preferred. The reactions may be conducted at subatmospheric pressure or superatmospheric pressure (viz., 60 Kg./m² - 2100 Kg./m² absolute), but ambient atmospheric pressure (about 10330 Kg./m², absolute) is most often used.

Endpoint determination - The completion of the reaction between the QAS and Nu may be determined by a number of conventional techniques. One method is to use thin layer chromatography to determine if the QAS is substantially removed from the reaction zones.

Sequence of Operation - The addition of the first and second reagents to the first reaction zone may take place in any order. For example, Nu may be initially added to the reaction zone followed by addition of the QAS, or vice versa. Alternatively, the first and second reagents may be simultaneously charged to each reaction zone.

When necessary, a solid-supported scavenger is added to the reaction mixture to bind the unreacted nucleophilic reagent. The amount of scavenger added to the reaction mixture is based on the scavenger's available functionality. The scavenger is added in at least an amount equal to the theoretical excess equivalents of unreacted scavenger. Preferably the solid supported scavenger is used in an amount that is from 1.25 to about 5 times the theoretical excess equivalents of unreacted second reagent. The reaction zone is maintained at a temperature for a time sufficient to permit reaction of the excess second reagent and the scavenger. Typically, the reaction requires only seconds but the selection of reaction conditions that may be used is the same as set out above.

The separation of the solid supported scavenger from the library compound dissolved in the solvent phase of the reaction may be done by any conventional chemical or physical method. Preferred are physical methods which are applicable to all members of a diverse library. Such methods include, for example: (i) ion exchange chromatography (ii) filtration, (iii) centrifugation, (iv) decantation, and (v) washing and any combination thereof. Filtration and ion exchange chromatography are particularly preferred forms of purification.

The purification last step of the process may optionally be supplemented by a solvent removal step in which the solute library compound is removed from its solvent by conventional processes known in the art; such as solvent evaporation, distillation, salting out, solvent extraction, and etc.

The library of compounds formed using the process of the invention can be used to screen for compounds with biological activity. A myriad of biological assays are known in the art and can be used to screen the library of compounds. Illustrative additional assays include, but are not intended to be limited to *in vitro* assays such as enzymatic inhibition, receptor-ligand binding, protein-protein interaction, and protein-DNA interaction; cell based, functional assays such as transcriptional regulation, signal transduction / second messenger, and viral infectivity; add, incubate & read assays such as scintillation proximity assays (SPA), fluorescence polarization assay, fluorescence correlation spectroscopy, colorimetric biosensors,

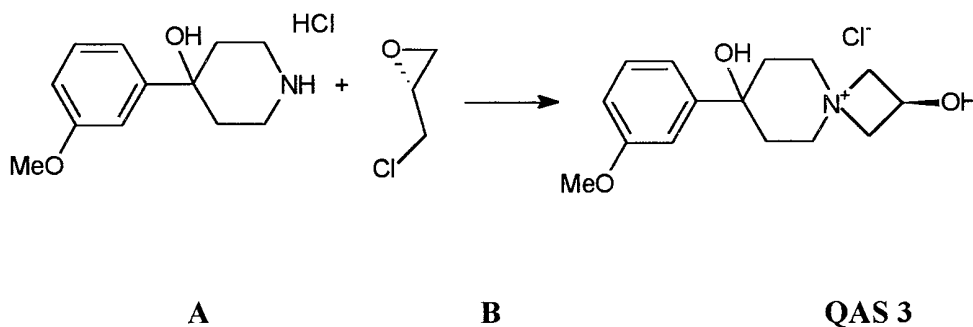
cellular reporter assays using reporter genes such as luciferase, green fluorescent protein, β -lactamase, and the like; and electrical cell impedance sensor assays. All of the above assays are known in the art to be predictive of success for an associated disease state.

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EXAMPLES

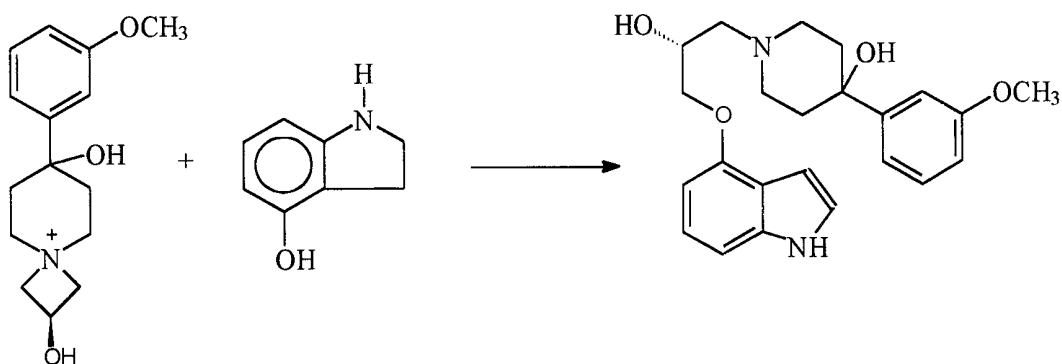
The following example are provided to demonstrate the underlying chemistry and processes of the present invention. The invention is not intended to be limited by these examples.

10 Example 1 - Synthesis of QAS



Compound **A** (described in U.S. Pat. Nos. 5,627,196 and 5,576,321) was dissolved in MeOH in a 250 mL round-bottom flask equipped with a magnetic stirrer, nitrogen bubbler, heat mantle, thermometer/thermowatch, and condenser. NaOH was added, a slurry formed and was stirred for 10 minutes, after which the epichlorohydrin **B** was added. The slurry was heated to 50°C and stirred at this temperature for 16 hours. The heat was removed, the reaction mixture cooled, dried with Na₂SO₄, and then concentrated. CH₂Cl₂ was added to the concentrate and the mixture was stirred for 2 hours at room temperature. The resulting crystalline solid was filtered, rinsed and dried at 45°C overnight (Yield 18 g, 90%; Chiral assay - 76% product isomer, 24 enantiomer = 52% enantiomeric excess).

Example 2



Compound A

Compound B

MW 299.8

MW 133.15

MW 396.49

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1.0 g of compound A and 0.46 g of compound B were mixed with 20 ml of acetone ,
 2.1 eq. of cesium carbonate and 0.05g of tetrabutylammonium bromide (TBAB - as
 catalyst). The mixture was placed in a 50 ml round bottom flask equipped with a
 magnetic stirrer, nitrogen bubbler, condenser and heat mantle. The mixture was heated
 and allowed to reflux for 3 hours. Thereafter 60 ml of ethyl acetate and 60 ml of water
 were added to the mixture. The layers were separated and the aqueous layer was
 washed again with 60 ml of ethyl acetate. The organic layers were combined and
 condensed to a dark oil. Yield 1.54 g, Potency = 58.5 % (68.2 % corrected yield),
 EE = 25.76% (62.88 % R-enantiomer, 37.12 % S-enantiomer (product C)). Product
 enriched in the opposite isomer can be obtained by starting with the opposite isomer
 (S-isomer) of the epichlorohydrin in forming the QAS intermediate.

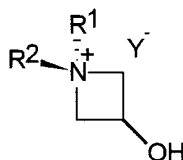
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It should be understood that a wide range of changes and modifications can be
 made to the embodiments described above. It is therefore intended that the foregoing
 description illustrates rather than limits this invention, and that it is the appended claims,
 including all equivalents, which define this invention.

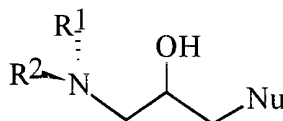
CLAIMS:

1. A process of stereoselective chemical synthesis which comprises reacting a nucleophilic agent and a chiral quaternary azetidinium salt (QAS) substrate of the formula (I):



where Y is a counterion, and where either R¹ and R² are different and are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, and 5-10 membered heterocyclic group containing at least one N, S or O; or wherein R¹ and R², together with the N which they substitute, form a 5-8 membered ring system containing 0, 1, 2, or 3 heteroatoms selected from NR³R⁴, O or S; and wherein each of R¹ and R² may be unsubstituted or substituted one to three times with a substituent selected from the group consisting alkyl, alkenyls, alkynyls, halogen, hydroxy, oxo, phosphoryl, thiol, sulfinyl, sulfonyl, aryl, 5-10 membered heterocyclic group containing at least one N, S or O, amine, imine, nitro, cyano, amidino, carbonyl; wherein the moieties substituted on the hydrocarbon chain can themselves be substituted with one to three further substituents;

in solution for a time sufficient to produce a compound of the formula (II)



where R¹ and R² are defined as above and Nu is a negative ion or a molecule that has an unshared pair of electrons.

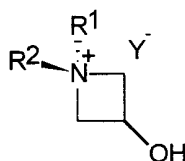
2. The process of claim 1, which produces a reaction product with an enantiomeric excess of greater than about 60%.

3. The process of claim 2, wherein the enantiomeric excess is greater than about 80%.

4. The process of claim 3, wherein the enantiomeric excess is greater than about 90%.

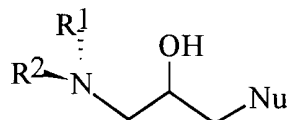
5. The process of claim 3, wherein Nu is selected from the group consisting of alkyl and aromatic thiols; alkyl and aromatic alcohols; aromatic heterocyclic compounds that contain a nucleophilic nitrogen; primary, secondary and tertiary amines; anilines; anionic carbon atoms; salts of halides; alkyl and aromatic phosphines; primary and secondary alkyl or aromatic hydrazines; alkyl and aromatic hydroxylamines; salts of cyanide anion; ammonia and salts of ammonia; salts of hydroxide anion; and cyclic hydrazines.

6. A chiral quaternary azetidinum salt (QAS) substrate of the formula (I):



where either R¹ and R² are different and are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, and 5-10 membered heterocyclic group containing at least one N, S or O; or wherein R¹ and R², together with the N which they substitute, form a 5-8 membered ring system containing 0, 1, 2, or 3 heteroatoms selected from NR³R⁴, O or S; and wherein each of R¹ and R² may be unsubstituted or substituted one to three times with a substituent selected from the group consisting alkyl, alkenyls, alkynyls, halogen, hydroxy, oxo, phosphoryl, thiol, sulfinyl, sulfonyl, aryl, 5-10 membered heterocyclic group containing at least one N, S or O, amine, imine, nitro, cyano, amidino, carbonyl; wherein the moieties substituted on the hydrocarbon chain can themselves be substituted with one to three further substituents.

7. An enantiomerically enriched compound of the formula (II)

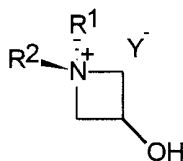


where either R^1 and R^2 are different and are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, and 5-10 membered heterocyclic group containing at least one N, S or O; or wherein R^1 and R^2 , together with the N which they substitute, form a 5-8 membered ring system containing 0, 1, 2, or 3 heteroatoms selected from NR^3R^4 , O or S; and wherein each of R^1 and R^2 may be unsubstituted or substituted one to three times with a substituent selected from the group consisting alkyl, alkenyls, alkynyls, halogen, hydroxy, oxo, phosphoryl, thiol, sulfinyl, sulfonyl, aryl, 5-10 membered heterocyclic group containing at least one N, S or O, amine, imine, nitro, cyano, amidino, carbonyl; wherein the moieties substituted on the hydrocarbon chain can themselves be substituted with one to three further substituents; and

Nu is a negative ion or a molecule that has an unshared pair of electrons.

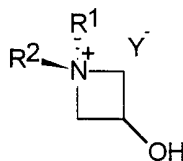
8. The enantiomerically enriched compound of claim 7, wherein Nu is selected from the group consisting of alkyl and aromatic thiols; alkyl and aromatic alcohols; aromatic heterocyclic compounds that contain a nucleophilic nitrogen; primary, secondary and tertiary amines; anilines; anionic carbon atoms; salts of halides; alkyl and aromatic phosphines; primary and secondary alkyl or aromatic hydrazines; alkyl and aromatic hydroxylamines; salts of cyanide anion; ammonia and salts of ammonia; salts of hydroxide anion; and cyclic hydrazines.

9. A vessel in which at least two chiral quaternary azetidinium salts (QAS) are physically separated from each other, wherein the QAS are of the formula (I):



where either R^1 and R^2 are different and are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, and 5-10 membered heterocyclic group containing at least one N, S or O; or wherein R^1 and R^2 , together with the N which they substitute, form a 5-8 membered ring system containing 0, 1, 2, or 3 heteroatoms selected from NR^3R^4 , O or S; and wherein each of R^1 and R^2 may be unsubstituted or substituted one to three times with a substituent selected from the group consisting alkyl, alkenyls, alkynyls, halogen, hydroxy, oxo, phosphoryl, thiol, sulfinyl, sulfonyl, aryl, 5-10 membered heterocyclic group containing at least one N, S or O, amine, imine, nitro, cyano, amidino, carbonyl; wherein the moieties substituted on the hydrocarbon chain can themselves be substituted with one to three further substituents.

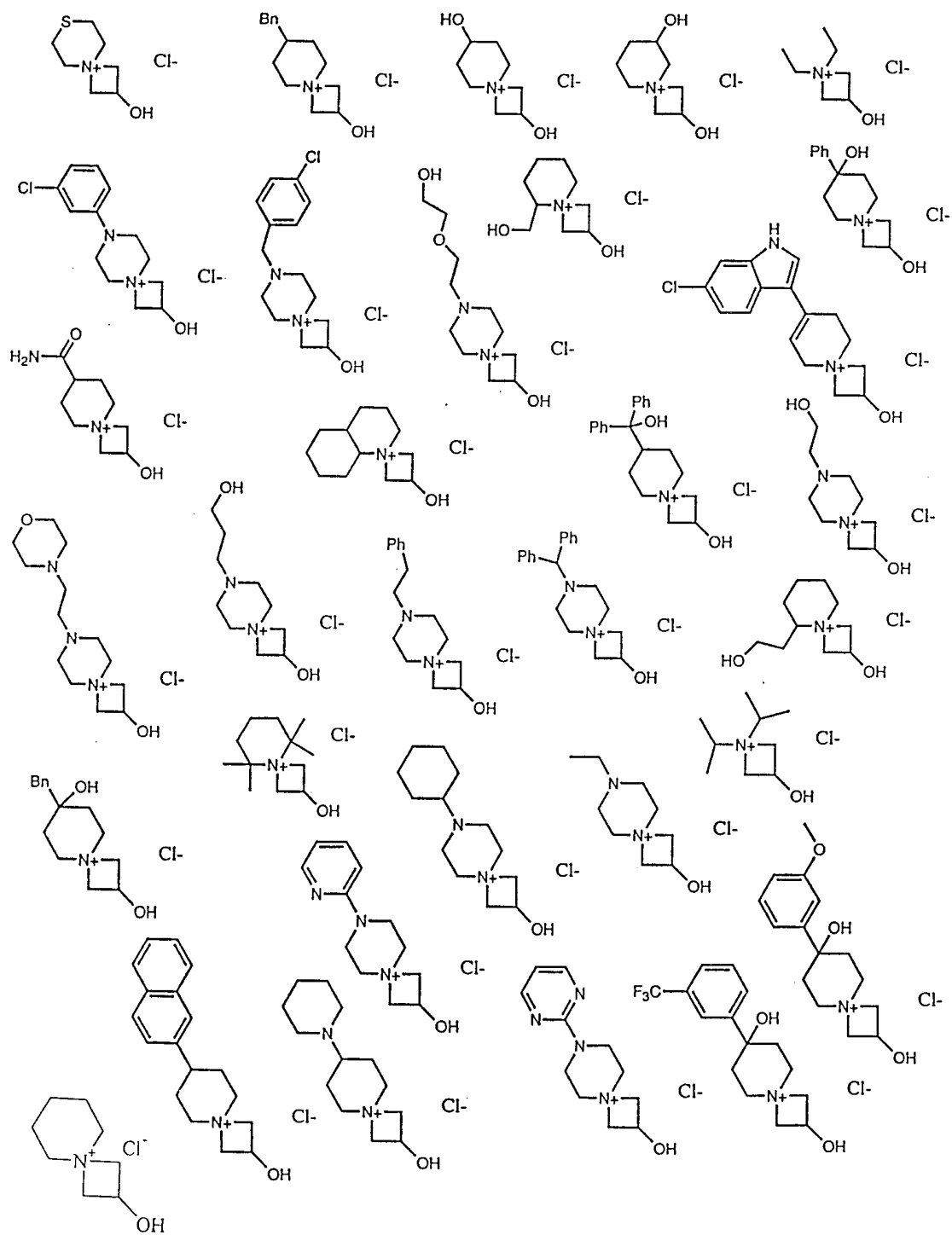
10. An apparatus suitable as a replacement element in an automated assay machine as a source of individual members of a library of structurally related compounds, said apparatus comprising a 2-dimensional array of defined reservoirs, each reservoir containing a compound of said library, where said structurally related compounds are chiral quaternary azetidinium salts (QAS) of the formula (I):



where either R^1 and R^2 are different and are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, and 5-10 membered heterocyclic group containing at least one N, S or O; or wherein R^1 and R^2 , together

with the N which they substitute, form a 5-8 membered ring system containing 0, 1, 2, or 3 heteroatoms selected from NR^3R^4 , O or S; and wherein each of R^1 and R^2 may be unsubstituted or substituted one to three times with a substituent selected from the group consisting alkyl, alkenyls, alkynyls, halogen, hydroxy, oxo, phosphoryl, thiol, sulfinyl, sulfonyl, aryl, 5-10 membered heterocyclic group containing at least one N, S or O, amine, imine, nitro, cyano, amidino, carbonyl; wherein the moieties substituted on the hydrocarbon chain can themselves be substituted with one to three further substituents.

Figure 1



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/31253

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07C 213/08; C07C 209/68; C07C 215/08; C07D 205/12

US CL : 564/487; 548/952; 564/503

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/487; 548/952; 564/503

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chem. Abstracts, Vol 61, 1964, (Columbus, OH, USA), abstracts 7008d and 7008f, ICHIKAWA, K. "Reactions of aliphatic amines with epoxypropane derivatives and their products, part I and II", Yuki Gosei Kagaku Kyokai Shi, 1964, 22(7), 546-52 and 553-60, see entire document.	6
X	MARTON-MERESZ ET AL. Synthesis of cytostatically active piperazine derivatives. Acta Chim. Hung. 1983, Vol. 112, No. 1, pages 31-4, especially compound 21 on page 36.	6
X	US 3,494,775 A (COSCIA ET AL) 10 February 1970 (10.2.1970), column 5 lines 9-26.	6
X	KRYUKOVA ET AL. Condensation of alkaloid ephedrine with epichlorohydrin. Dokl. Akad. Nauk Tadzh. SSR, Vol 10, No. 7, July 1967, see pages 26-29 especially figure on page 26.	6
X	JP 41-4981 A (YAMANOUCHI PHARMACEUTICAL) 18 March 1966 (18.3.66) see figure 1.	6
X	JP 41-19972 A (YAMANOUCHI PHARMACEUTICAL) 19 November 1963 (11.11.63) see figure 1.	6
X	US 5,576,321 (KRUSHINSKI, JR. ET AL) 19 November 1996 (19.11.1996), see columns 37 and 38, example 34.	7 & 8



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:		"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

13 March 2000 (13.03.2000)

Date of mailing of the international search report

07 JUN 2000

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Thomas C. McKenzie

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/31253

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 1,456,525 (IMPERIAL CHEMICAL INDUSTRIES LIMITED) 24 November 1976 (24.11.76) see claim 1.	1-5
A	HIGGINS, R. H. ET AL. Ring Opening of Azetidinols by Phenols: Regiochemistry and Stereochemistry. J. Org. Chem., 1994, Vol. 59, No. 8, pages 2172-2178.	1-5

INTERNATIONAL SEARCH REPORT

International application No.

PC JS99/31253

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-8

Remark on Protest☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/31253

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-6, drawn to a stereospecific ring opening process of chiral azetidinium salts and the chiral salts, thus a reagent and its method of use.

Group II, claim(s) 7 and 8, drawn to the known products of this process.

Group III, claim(s) 9, drawn to a vessel containing the reagent is at least two compartments.

Group IV, claim(s) 10, drawn to an apparatus for making libraries.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature is the chiral ring opening reaction. Applicants' contribution to the art is the process of making known compounds. The apparatus may be used with other molecules.

Continuation of B. FIELDS SEARCHED Item 3: SCISEARCH Gaertner, CAS
CA-REG substructure search