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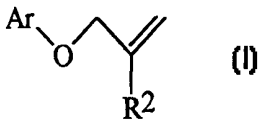
(57) Abstract

This invention relates to a process for producing a plurality of olefin compounds of formula (I). The method is ideal for generating libraries of compounds for high throughput screening. The invention also provides a library of above compounds physically separated from one another in a reaction vessel. This library is useful for optimizing the activity of therapeutically useful compounds.



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SOLUTION PHASE SYNTHESIS OF OLEFINS AND OLEFIN-DERIVED PRODUCTS

BACKGROUND OF THE INVENTION

The present invention relates to the generation of a plurality of olefins and olefin derived products.

Therapeutic drugs frequently contain similar structural and/or functional groups. In the search for new, more effective drugs, it is desirable to synthesize a library of chemical compounds that contain these groups or are otherwise structurally or functionally similar to known pharmaceutical agents. However, the synthesis of structural or functional analogs on an individual basis is slow and highly inefficient due to the vast number of potential permutations.

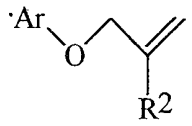
Combinatorial chemistry can be an efficient and innovative way to generate a large number of structurally related compounds for drug discovery purposes. One objective of combinatorial chemistry is to find a structural building block, or template, that can be methodically manipulated to produce a library of distinct compounds that contain a common or similar structure or functionality. An optimal template can be derivatized with a variety of different substituents, independent of previous transformations, and thereby maximize the scope of the library.

Compounds containing amine functional groups have known biological activity. Allylic amines are known to have activity in the Central Nervous System (CNS). For example, the antidepressant PROZAC® and the anti-schizophrenia drug ZYPREXA® are known CNS agents and can be derived from allylic amines. Additionally, aliphatic

amines are more broadly useful in drug discovery. One method of synthesizing amines is through the amination of an olefin.

SUMMARY OF THE INVENTION

One aspect of the present invention is directed to a process for simultaneously preparing a plurality of different olefin compounds of the formula (I):



(I)

where Ar is a substituted or unsubstituted aryl or heteroaromatic group, and R^2 is a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaromatic, or heterocyclic ring.

In a first embodiment, the process comprises the steps of reacting in solution a hydroxyaromatic having the formula ArOH with a 2,3-dihaloalkene, wherein Ar is defined above, so as to form a 2-halo-3-alkoxy-alkene solution; providing a plurality of different boronic acids, esters, or alkyl boranes, each having the general formula $R^2B(R^3)_2$, wherein R^2 is defined above and R^3 is either hydroxy, alkoxy, or alkyl, and reacting each of the plurality of different boronic acids, esters, or alkyl boranes with a suitable metal catalyst and portion of the 2-halo-3-alkoxy alkene solution for a time sufficient to produce a plurality of different compounds of the formula (I). Preferably the 2,3-dihaloalkane is 2,3-dibromopropene.

In a second embodiment, said process comprises the steps of providing a plurality of different hydroxyaromatics having the formula ArOH, wherein Ar is defined above; reacting in solution each of said plurality of different of hydroxyaromatics with a 2,3-

dihaloalkene, so as to form a plurality of 2-halo-3-alkoxy-alkenes; providing a boronic acid, ester, or alkyl borane having the formula $R^2B(R^3)_2$, wherein R^2 is defined above and R^3 is either hydroxy, alkoxy, or alkyl; and reacting each of the plurality of different of 2-halo-3-alkoxy-alkenes with said boronic acid for a time sufficient to produce a plurality of different compounds of the formula (I). Preferably the 2,3-dihaloalkane is 2,3-dibromopropene.

In another aspect of the present invention, the olefin compounds, as synthesized in the first or second embodiment, are aminated. In one embodiment the olefins are reacted with an oxidant so as to form an epoxide and the epoxide is then opened with a primary or secondary amine. In another embodiment, the olefins are subjected to hydroboration followed by amination. In another embodiment, the olefins participate in a three component hetero Diels Alder reaction.

"Alkyl" (or alkyl- or alk-) means a straight or branched chain hydrocarbon. The hydrocarbon preferably contains 1 to 20, more preferably 1 to 6, carbon atoms.

"Alkene" or "olefin" means a straight or branched chain unsaturated hydrocarbon that contains at least one double bond.

"Alkoxy" means a group having the general formula -OR, wherein R is any alkyl or aryl group.

"Aryl" or "aromatic" means a substituted or unsubstituted, mono- or bicyclic carbocyclic aromatic ring preferably containing 6 to 10 carbon atoms, such as phenyl (Ph) or naphthyl.

"Halo" means a halogen atom, such as chlorine, fluorine, iodine or bromine.

"Haloalkene" means a straight or branched chain unsaturated alkene containing at least one halogen atom substituent and at least one double bond.

"Heteroaromatic" means an aryl or aromatic group wherein one or more members of the aromatic ring is a heteroatom, preferably oxygen, nitrogen or sulfur.

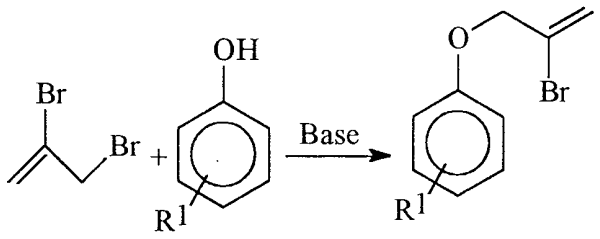
"Heterocyclic" means a cyclic hydrocarbon wherein one or more members of the ring is a heteroatom, preferably oxygen, nitorgen or sulfur.

"Substituted" means that the moiety contains at least one, preferably 1-3 substituent(s). These substituents can optionally be further substituted with 1-3 substituents. Examples of substituted substituents include carboxamide, alkylmercapto, alkylsulphonyl, alkylamino, dialkylamino, carboxylate, alkoxycarbonyl, alkylaryl, aralkyl, alkylheterocyclic ring, etc. Suitable substituents include hydrogen, hydroxyl, amino, oxy, carbonyl, thiol, alkyl, alkenyl, alkynyl, alkoxy, halo, nitrile, nitro, aryl and heterocyclic ring.

"Vinyl halide" means an alkene wherein at least one of the four substituents directly linked to the olefin is a halogen.

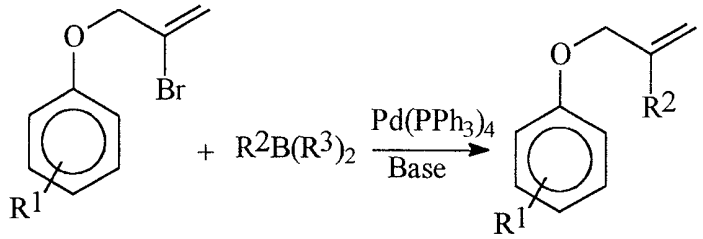
DETAILED DESCRIPTION OF THE INVENTION

The olefin compounds of the present invention are produced by a two-step reaction sequence. In the first reaction a 2,3-dihaloalkyl is reacted with a hydroxyaromatic to yield an allyl ether vinyl halide, Equation (II):



(II)

The resulting aromatic vinyl halide is subjected to the second step, a Suzuki coupling reaction. The Suzuki coupling reaction is generally described in Miyaura, N.; Suzuki, A. *Palladium-catalyzed cross-coupling reactions of organoboron compounds*, Chem Rev. 1995, 95, 2457-2483, which is hereby incorporated by reference in its entirety. The vinyl halide is cross-coupled with a boronic acid to yield bis-functionalized olefins, Equation (III):



(III)

A library of olefin compounds is synthesized utilizing the above reactions. Diversity is introduced by varying the substituents, Ar and R^2, so as to create plurality of distinct compounds that have a related structure or functionality.

Haloalkene

Preferred haloalkenes are short chain, di-halo substituted alkenes. The length of the alkene chain and the choice of the halogen substituents is governed by the ability of the haloalkene to undergo nucleophilic attack by the hydroxyaromatic followed by subsequent transition metal-mediated cross coupling reaction with a suitable boronic acid, ester, or alkyl borane. Other halogens, such as iodine and chlorine may be used in place of bromine. Additionally, trifluoromethanesulfonate may be substituted for any one of these halogen atoms and is a suitable substituent. The length, size and structure of the alkene chain is subject to a variety of permutations. Longer, branched and/or substituted alkenyl chains may be used if the structure does not preclude nucleophilic attack by a hydroxyaromatic and subsequent cross-coupling. The non-halogen substituents of the double bond may be any of the substituents defined above. Preferably, the substituents of the double bond are short chain alkyl groups. More preferably, one of the olefin carbons remains unsubstituted. The most preferred alkyl halide is 2,3-dibromopropene.

Hydroxyaromatic

Suitable hydroxyaromatics may be substituted or unsubstituted, and may include electron donating and electron-withdrawing substituents, and/or alkyl groups. Suitable hydroxyaromatics may also be polycyclic aromatics or heteroaromatics. Preferably, the hydroxyaromatic is a substituted or unsubstituted phenol.

Boronic Acid

The boronic acid may be any alkyl, alkenyl, heteroaryl or aryl boronic acid, ester or alkyl borane. Preferably, the boronic acid or ester is an aryl boronate. Most

preferably, the boronic acid has the general formula $R^2B(OH)_2$ wherein R^2 is a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclic ring.

General Process

Allyl Ether Vinyl Halide Synthesis

In general, the di-haloalkene is reacted with the hydroxyaromatic in solvent for a time and at a temperature sufficient to result in the allyl ether product. Common dihaloalkenes, such as 2,3-dibromopropene, are commercially available. Alternatively, a general synthesis that may be used to synthesize n, n+1-dihaloalkenes is described in Nishiyama, H.; Yokoyama, H.; Narimatsu, S.; Itoh, K.; Tetrahedron Lett 1982, 23 (12), 1267, which is hereby incorporated by reference in its entirety.

Suitable solvents include, but are not limited to, tetrahydrofuran (THF), dimethylformamide (DMF), dimethylsulfoxide (DMSO), dioxane, CH_2Cl_2, toluene, acetonitrile, chloroform, ethyl acetate or acetone, or mixtures thereof. In some instances, the reaction can be conducted in mixed solvent systems which contain alcohol. The preferred solvent is acetone.

The reaction is preferably conducted until the starting dihaloalkene is consumed.

The reaction is preferably conducted between room temperature (ca. 22°C) and the reflux point of the solvent used. More preferably, the reaction is conducted at room temperature.

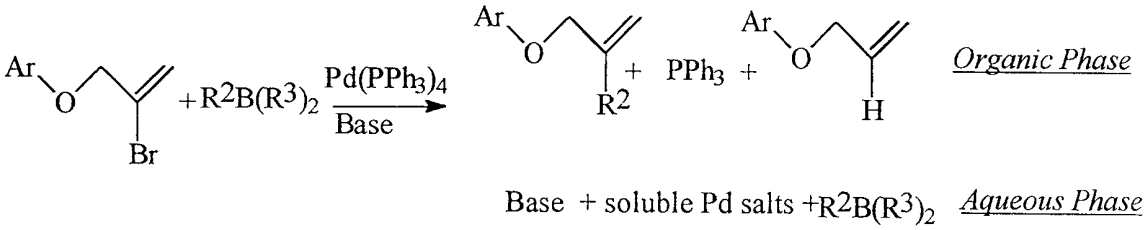
The reaction is carried out under basic conditions, preferably using solid phase bases such as PTBD (polystyrene 1,5,7-triazabicyclo[4.4.4.0]dec-5-ene)or anion exchange resins. Alternatively, traditional bases such as sodium hydroxide or sodium bicarbonate may be used so long as the base is a worse nucleophile than the aryl oxide

salt of the corresponding hydroxyaromatic. Generally, a suitable base will be able to deprotonate the hydoxyaromatic without forming a soluble halide salt.

The vinyl halide product can be separated from starting material using any conventional method. Preferably, the mixture is filtered and the solvent evaporated to yield the vinyl halide. More preferably, the filtered solution containing the allylic ether is submitted to subsequent reaction without evaporation of solvent.

Olefin Synthesis

In general, the vinyl halide is reacted with the boronic acid, ester, or alkyl borane in solution, under basic conditions and in the presence of a catalyst for a time and at a temperature sufficient to result in product. This synthesis is known as a Suzuki coupling reaction. The synthesis and subsequent separation is shown in Equation (IV) and described below.



(IV)

Suitable solvents for the olefin synthesis include, but are not limited to, tetrahydrofuran (THF), dimethylformamide (DMF), dimethylsulfoxide (DMSO), dioxane, CH_2Cl_2, toluene, acetonitrile, chloroform, ethyl acetate or acetone, or mixtures thereof. In some instances, the reaction can be conducted in mixed solvent systems which contain alcohol. The preferred solvent is acetone.

The reaction is preferably conducted until the starting vinyl halide is consumed.

The reaction is preferably conducted at room temperature (ca. 22°C) to the reflux point of the solvent used. More preferably, the reaction is conducted at about 50-55°C.

The reaction is carried out under basic conditions. The preferred base is CsF, but other fluoride bases or traditional Suzuki bases such as potassium hydroxide, potassium carbonate, or sodium bicarbonate as well as resin bound bases such as PTBD may be used.

A suitable catalyst is used. Examples include, but are not limited to, palladium or nickel catalysts, with a variety of ligands including triphenyl arsine, 2-pyridyl diphenylphosphine or trifuryl phosphine. Most preferably, the catalyst is palladium tetrakis (triphenyl phosphine).

In a preferred embodiment, an expedited method is used for removing the by-products and excess reagents utilized in the Suzuki reaction. It is preferred that the reaction is quenched with water. The desired organic products may then be extracted into dichloromethane. The resultant biphasic mixture can be separated into organic and aqueous soluble components by means of expedited liquid phase separation techniques such as filtration through a hydrophobic membrane or more preferably a diatomaceous earth column. Diatomaceous earth columns, available from Varian, act to retain the aqueous phase and any dissolved materials. In addition, insoluble materials such as spent palladium catalyst will remain at the top of the column. Most components of the Suzuki products will be either insoluble in the dichloromethane/water mixture and will be removed by filtration or will be extremely hydrophilic and will be dissolved in the aqueous and retained on diatomaceous earth.

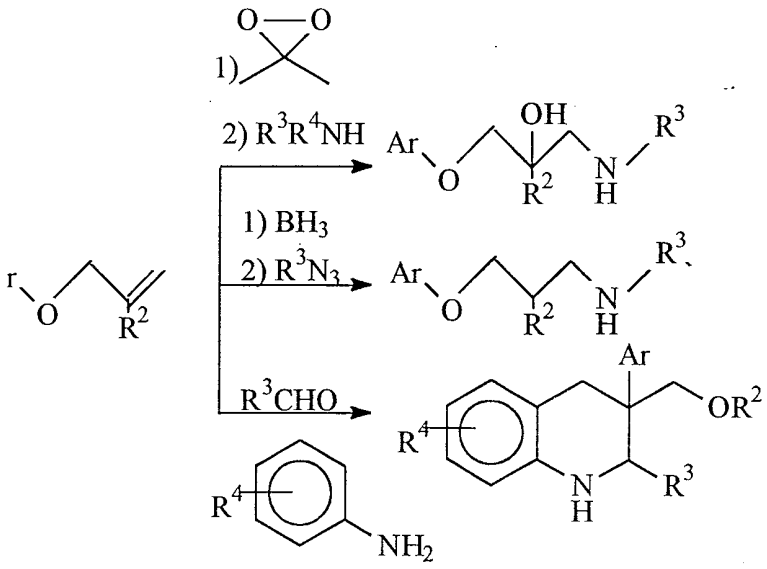
Preferably, the ligand on the palladium does not contain an olefin moiety so that further reaction sequences which depend on the presence of an olefin will be able to distinguish product from ligand. The use of a water soluble ligand such as 2-pyridyl diphenylphosphine will decrease the amount of ligand in the organic phase.

Amine Synthesis

The olefins thus synthesized serve as templates for further functionalizations, preferably to amines. Reactions with these olefins to facilitate further functionalizations are well described in the literature. Exemplary literature references are listed below, each of which is hereby incorporated by reference in its entirety. Generally, the opening of epoxides derived from olefins with amines in a combinatorial format is described in A. J. Shuker, M. G. Siegel, D. P. Matthews, L. O. Weigel, "*The Application of High-Throughput Synthesis And Purification To The Preparation Of Ethanolamines,*" Tetrahedron Lett. 1997, 38, 6149-6152. The epoxidation of olefins with dimethyldioxirane are generally described in Halcomb, R. L.; Danishefsky, S. J.; J Am Chem Soc 1989, 111, 6661. The hydroboration-amination of olefins is generally described in H.C. Brown, M. M. Midland, and A. B. Levy, "*Facile Reaction of Alkyl- and Aryldichloroboranes with Organic Azides. A General Stereospecific Synthesis of Secodary Amines,*" J. Am. Chem. Soc 1973, vol. 95, pp. 2394-2396, and also H.C. Brown, A.M. Salunkhe, and B. Singaram, "*Chiral Synthesis via Organoboranes. 28. Reaction of alpha-Chiral Organyldichloroboranes with Organyl Azides Providing a Synthesis of Secondary Amines with Exceptionally High Enantiomeric Purities,*" J. Org. Chem 1991, vol. 56, pp. 1170-1175. Amination utilizing the hetero-Diels Alder reaction is generally described in S. Kobayashi and S. Nagayama, *"A New Methodology for Combinatorial Synthesis. Preparation of Diverse Quinoline Derivatives Using a Novel Polymer-Supported Scandium Catalyst,*" J. Am. Chem. Soc. 118 (1996) 8977-8978.

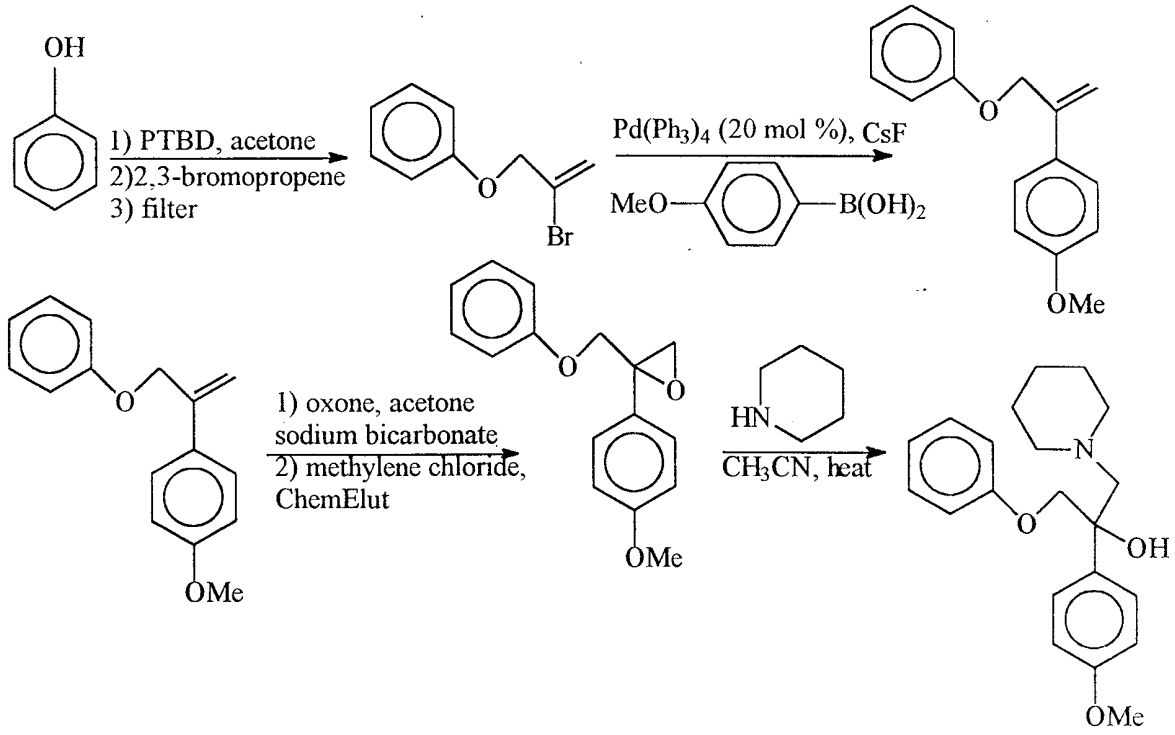
Specific examples of amination reactions are described below in Equation (V). Treatment of the olefin with an oxidant, such as dimethyldioxirane, and sodium bicarbonate will produce an epoxide which can be subsequently opened by an amine. Alternatively, hydroboration followed by amination will lead to a similar secondary

amine. Further, the olefin may serve as the dieneophile component in a 3-component hetero-Diels Alder reaction. Another means of functionalizing an olefin to an amine is through reductive cleavage of a benzylic alcohol to reveal non-carbinol products.



(V)

A specific example of a preferred amine synthesis is provided in Equation (VI), and described below.



(VI)

In Equation (VI) phenol is deprotonated using PTBD resin. This resin mixture is then treated with 2,3-dibromopropene to give vinyl bromide cleanly in ~80% yield. This material is filtered directly into a round bottom flask containing the reagents for a Suzuki coupling reaction: $Pd(PPh_3)_4$ (20 mol %), CsF, and 4-methoxyphenylboronic acid. The mixture is heated in acetone as solvent until all of the starting vinyl bromide is consumed. The entire reaction mixture is then poured directly into an aqueous acetone solution of dimethyldioxirane, generated from addition of a basic aqueous solution of OXONE® to acetone. Upon complete consumption of the olefin, the reaction is diluted with methylene chloride and passed through a Varian CHEM ELUT ™ column containing diatomaceous earth. The methylene chloride eluent is evaporated to give clean epoxide. This epoxide is opened cleanly with piperidine in acetonitrile to give the corresponding ethanolamine product after ion exchange chromatography.

Dimethyldioxirane is the preferred oxidant for epoxide formation, but other oxidants known to effect epoxidation may be used, such as m-CPBA (meta-chloroperbenzoic acid) or peroxide. Any aliphatic primary or secondary amine may be used to open the epoxide. The epoxide opening may be performed in DMSO, DMF, methanol, ethanol, isopropanol, or acetonitrile as solvent.

Combinatorial Synthesis

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

For small scale synthesis of multiple products, the process of the invention is preferably carried out in containers adapted for parallel array synthesis. With parallel array synthesis, individual reaction products are prepared in each of multiple reaction zones. The reaction zones are physically separated from one another in a reaction vessel.

A preferred embodiment of the present invention is a diverse olefin 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 olefin 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, or FLEXCHEM ™ 96 well Synthesis Assembly available from Robbins Scientific.

Typically, the wellplate apparatus is in the form of a rigid or semi-rigid plate. Preferably, the plate has a common surface containing openings of a plurality of reservoirs 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, or reservoirs, 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.

Preferably, each of the plurality of compounds is tested for biological activity. For example, one method of testing for biological activity using serotonin binding assays is described in L. M. Gaster, et al. "*The Selective 5-HT1B Receptor Inverse Agonist 1'-Methyl-5-[[2'-methyl-4'-95-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]carbonyl]-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine] (SB-224289)Potently Blocks Terminal 5-HT Autoreceptor Function Both in Vitro and in Vivo*," J. Med. Chem. 1998, vol. 41, pp. 1218-1235.

EXAMPLES

The following examples are provided to demonstrate the underlying chemistry of the process of the present invention. The invention is not limited by these examples.

General Process

2-Halo-3-Aryloxypropene

To a suspension of PTBD (286 mg, 0.63 mmol) resin in acetone (3 mL) is added an acetone (2 mL) solution of 2,3-dibromopropene (100 mg, 0.50 mmol) and phenol (0.25 mmol). The reaction mixture is allowed to stir at 22°C for 15 hours. Following that time, the mixture is filtered and the solvent evaporated to yield the aryloxypropene product, which requires no further purification.

2-Aryl-3-Aryloxypropene

A nitrogen purged flask is charged with $Pd(PPh_3)_4$ (5-20 mol %), CsF (87 mg, 0.57 mmol) and the arylboronic acid (0.35 mmol). To this mixture is added an acetone (3mL) solution of 2-bromo-3-aryloxypropene (0.23 mmol) and the resulting solution is stirred at 50-55°C until the reaction is deemed sufficiently complete by TLC analysis (3-5 hours). The reaction is then diluted with water and Et_2O (3 mL each), the aqueous layer extracted several times with Et_2O (10 mL total) and the combined organic extracts dried over $MgSO_4$ or Na_2SO_4. The crude reaction mixture is then purified by column chromatography using silica gel and an Et_2O/pentane solvent mixture as the eluent.

Epoxidation of 2-aryl-3aryloxypropene

The 2-aryl-3-aryloxypropene (0.21 mmol) is dissolved in acetone (1 mL). To this solution is added dimethyldioxirane (5 mL of a 0.05 M solution, 0.25 mmol) and the resulting mixture is allowed to stir at 22°C until the reaction is deemed complete by TLC analysis (approximately 6 hours). Evaporation of the solvent yields the epoxy-propane, which requires no further purification.

Specific Example (1)

2,3-dibromopropene (100 mg, 0.5 mmol) and phenol (23.5 mg, 0.25 mmol) are dissolved in acetone (5 mL) and allowed to stir in the presence of PTBD resin (286 mg, 0.63 mmol) at 22°C for 15 hours. This mixture is then filtered directly into a nitrogen purged flask charged with 4-methoxyphenylboronic acid (24.3 mg, 0.19 mmol), CsF (85 mg, 0.56 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol). The resulting mixture is then heated to 55°C until the reaction is deemed complete by TLC analysis (3-5 hours). When complete, Na_2EDTA is added to the Suzuki reaction and the entire crude mixture is then poured into a preformed 0°C OXONE ™ (1.42 g, 4.5 mmol)/$NaHCO_3$ (0.76, 9.4 mmol), acetone (5 mL)/ water (5 mL) mixture. The reaction is stirred at 0°C until deemed complete by TLC analysis (1-2 hours). When complete, the epoxidation reaction mixture is diluted with water (10 mL) and CH_2Cl_2 (10 mL) and the organic phase is then passed through a Varian CHEM ELUT ™ column followed by solvent evaporation. The residue is then reconstituted in CH_3CN (2 mL) and piperidine (106 mg, 1.25 mmol) is added to the solution. The reaction mixture is allowed to stir at 55°C for 3 hours. Evaporation yielded a dark oil that contained the amino-alcohol.

Specific Example (2)

A nitrogen purged flask is charged with $Pd(PPh_3)_4$ (25 mg, 0.023 mmol), CsF (105 mg, 0.69 mmol) and phenylboronic acid (56 mg, 0.46 mmol). To this mixture is added an acetone (3 mL) solution of 2-bromo-3-phenoxypropene (50 mg, 0.23 mmol) and the resulting solution is stirred at 50-55°C until the reaction is deemed complete by TLC analysis (3-5 hours). When complete, the crude mixture is then poured into a preformed 0°C OXONE ™ (1.42 g, 4.5 mmol)/$NaHCO_3$ (0.76, 9.4 mmol), acetone (3 mL)/ water (3 mL) mixture. The reaction is stirred at 0°C until deemed complete by TLC analysis (1-2

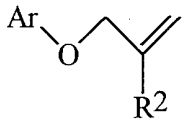
hours). When complete, the epoxidation reaction mixture is diluted with water (10 mL) and CH_2Cl_2 (10 mL) and the organic phase is then passed through a Varian CHEM ELUT ™ column followed by solvent evaporation. The residue is then reconstituted in CH_3CN (2 mL) and piperidine (16 mg, 0.19 mmol) is added to the solution. The reaction mixture is allowed to stir at 55°C for 15 hours. Following that time, the crude reaction mixture is diluted with a 5% HOAc/MeOH solution (2 mL) and passed through a Varian SCX BOND-ELUT ™ column (pre-wetted with 5 mL HOAc/ MeOH solution). The column is then washed several times with MeOH, followed by a 0.5 M NH3/MeOH solution (1mL) to release the amino-alcohol. Evaporation of the solvents yields a tan oil (14 mg, 20%).

* * * * *

Of course, 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 following claims, including all equivalents, which define this invention.

CLAIMS:

1. A process for simultaneously preparing a plurality of different compounds of the formula (I):



(I)

where Ar is an aryl or heteroaryl group which can be substituted or unsubstituted; and

R^2 is a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclic ring;

wherein said process comprises the steps of:

a) reacting in solution a hydroxyaromatic having the formula ArOH with a 2,3-dihaloalkene, wherein Ar is defined above, so as to form a 2-halo-3-alkoxy-alkene solution;

b) providing a plurality of different boronic acids, esters, or alkyl boranes, each having the general formula $R^2B(R^3)_2$, wherein R^2 is defined above and R^3 is an alkoxy, hydroxy, or alkyl group; and

c) reacting each of the plurality of different boronic acids, esters, or alkyl boranes with a portion of the 2-halo-3-alkoxy alkene solution and a suitable transition metal catalyst for a time sufficient to produce a plurality of different compounds of the formula (I).

2. The process of claim 1 wherein step (c) is conducted in solution in an array, such that each of the plurality of different boronic acids, esters, or alkyl boranes is

mixed with the 2-halo-3-alkoxy-alkene and a suitable transition metal catalyst in a physically separated area.

3. The process of claim 2 wherein the array is a wellplate apparatus.

4. The process of claim 1 wherein the halogen substituent of the 2,3-dihaloalkene is selected from the group consisting of bromine, chlorine and iodine.

5. The process of claim 1 wherein the 2,3-dihaloalkene is 2,3-dibromopropene.

6. The process of claim 1 wherein the transition metal catalyst is $Pd(PPh_3)_4$.

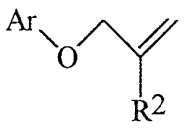
7. The process of claim 1 wherein the boronic acid has the general formula $R^2B(OH)_2$.

8. The process of claim 1 wherein Ar is a substituted aryl group.

9. The process of claim 1 wherein Ar is a phenyl group.

10. The process of claim 1 wherein R is a substituted alkyl group.

11. A process for simultaneously preparing a plurality of different compounds of the formula (I):



(I)

where Ar is an aryl or heteroaryl group which can be substituted or unsubstituted; and

R^2 is a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclic ring;

wherein said process comprises the steps of:

a) providing a plurality of different hydroxyaromatics having the general formula ArOH, wherein Ar is defined above;

b) reacting in solution each of the plurality of different hydroxyaromatics with a 2,3-dihaloalkene, so as to form a plurality of different of 2-halo-3-alkoxy-alkenes;

c) providing a boronic acid having the formula $R^2B(R^3)_2$, wherein R^2 is defined above and R^3 is alkoxy, hydroxy, or alkyl; and

d) reacting each of the plurality of different 2-halo-3-alkoxy-alkenes with said boronic acid, ester, or alkyl borane and a suitable transition metal catalyst for a time sufficient to produce a plurality of different compounds of the formula (I).

12. The process of claim 11 wherein steps (b) and (d) are conducted in an array, such that each reaction occurrs in a physically separated area.

13. The process of claim 12 wherein the array is a wellplate apparatus.

14. The process of claim 11 wherein the halogen substituent of the 2,3-dihaloalkene is selected from the group consisting of bromine, fluorine and iodine.

15. The process of claim 11 wherein the 2,3-dihaloalkene is 2,3-dibromopropene.

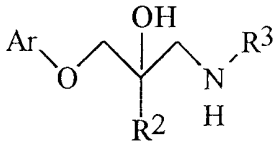
16. The process of claim 11 wherein the transition metal catalyst is $Pd(PPh_3)_4$.

17. The process of claim 11 wherein the boronic acid has the general formula $R^2B(OH)_2$.

18. The process of claim 1 wherein Ar is a phenyl group.

19. The process of claim 1 wherein R is a substituted alkyl group.

20. A process for simultaneously preparing a plurality of different compounds of the formula (I):



(I)

where Ar is an aryl or heteroaryl group which can be substituted or unsubstituted; and

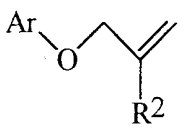
R^2 and R^3 are substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclic rings;

wherein said process comprises the steps of:

a) reacting in solution a hydroxyaromatic having the formula ArOH with a 2,3-dihaloalkene, wherein Ar is defined above, so as to form a 2-halo-3-alkoxy-alkene solution;

b) providing a plurality of different boronic acids, esters, or alkyl boranes, each having the general formula $R^2B(R^4)_2$, wherein R^2 is defined above and R^4 is alkoxy, hydroxy, or alkyl;

c) reacting each of the plurality of different boronic acids, esters, or alkyl boranes with a portion of the 2-halo-3-alkoxy alkene solution and a suitable transition metal catalyst for a time sufficient to produce a plurality of different compounds of the formula (II):

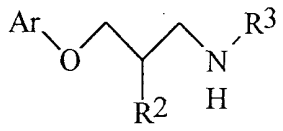


(II)

d) reacting the plurality of different compounds of the formula (II) with an oxidant and a metal bicarbonate, wherein the oxidant is selected from the group consisting of dimethyloxirane, m-CPBA or peroxides to form epoxides; and

e) reacting the epoxide with a primary or secondary amine to produce a plurality of different compounds of the formula (I).

21. A process for simultaneously preparing a plurality of compounds of the formula (I):



(I)

where Ar is an aryl or heteroaryl group which can be substituted or unsubstituted; and

R^2 and R^3 are a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclic rings;

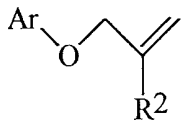
wherein said process comprises the steps of:

a) reacting in solution a hydroxyaromatic having the formula ArOH with a 2,3-dihaloalkene, wherein Ar is defined above, so as to form a 2-halo-3-alkoxy-alkene solution;

b) providing a plurality of different boronic acids, esters, or alkyl boranes, each having the general formula $R^2B(R^4)_2$, wherein R^2 is defined above and R^4 is alkoxy, hydroxy, or alkyl;

c) reacting each of the plurality of different boronic acids, esters, or alkyl boranes with a portion of the 2-halo-3-aryl alkene solution and a suitable transition metal

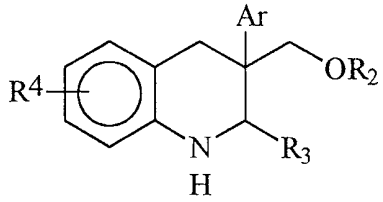
catalyst for a time sufficient to produce a plurality of different compounds of the formula (II); and



(II)

d) subjecting each of the plurality of products of the formula (II) to hydroboration amination to yield a plurality of different compounds of the formula (I).

22. A process for simultaneously preparing a plurality of different compounds of the formula (I):



(I)

where Ar is an aryl or heteroaryl group which can be substituted or unsubstituted; and

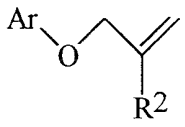
R^2 and R^3 are a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclic rings;

wherein said process comprises the steps of:

a) reacting in solution a hydroxyaromatic having the formula ArOH with a 2,3-dihaloalkene, wherein Ar is defined above, so as to form a 2-halo-3-alkoxy-alkene solution;

b) providing a plurality of different boronic acids, esters, or alkyl boranes, each having the general formula $R^2B(R^4)_2$, wherein R^2 is defined above and R^4 is alkoxy, hydroxy, or alkyl;

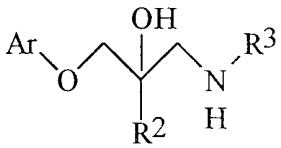
c) reacting each of the plurality of different boronic acids with a portion of the 2-halo-3-alkoxy alkene solution and a suitable transition metal catalyst for a time sufficient to produce a plurality of different compounds of the formula (II), and



(II)

d) subjecting each of the plurality of products of the formula (I) to a three component hetero Diels Alder reaction to form a plurality of different compounds of the formula (I).

23. A process for simultaneously preparing a plurality of different compounds of the formula (I):



(I)

where Ar is an aryl or heteroaryl group which can be substituted or unsubstituted; and

R^2 and R^3 are substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclic rings ;

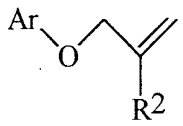
wherein said process comprises the steps of:

a) providing a plurality of different hydroxyaromatics having the general formula ArOH, wherein Ar is defined above;

b) reacting in solution each of the plurality of different hydroxyaromatics with a 2,3-dihaloalkene, so as to form a plurality of different of 2-halo-3-alkoxy-alkenes;

c) providing a boronic acid, ester, or alkyl borane having the formula $R^2B(R^4)_2$, wherein R^2 is defined above and R^4 is alkoxy, hydroxy, or alkyl;

d) reacting each of the plurality of different 2-halo-3-alkoxy-alkenes with said boronic acid, ester, or alkyl borane and a suitable transition metal catalyst for a time sufficient to produce a plurality of different compounds of the formula (II):

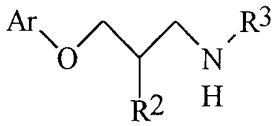


(II)

e) reacting the plurality of different compounds of the formula (II) with an oxidant and a metal bicarbonate, wherein the oxidant is selected from the group consisting of dimethyloxirane, m-CPBA or peroxides to form an epoxide; and,

f) reacting the epoxide with a primary or secondary amine to produce a plurality of different compounds of the formula (I).

24. A process for simultaneously preparing a plurality of compounds of the formula (I):



(I)

where Ar is an aryl or heteroaryl group which can be substituted or unsubstituted; and

R^2 and R^3 are a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclic rings;

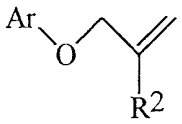
wherein said process comprises the steps of:

a) providing a plurality of different hydroxyaromatics having the general formula ArOH, wherein Ar is defined above;

b) reacting in solution each of the plurality of different hydroxyaromatics with a 2,3-dihaloalkene, so as to form a plurality of different of 2-halo-3-alkoxy-alkenes;

c) providing a boronic acid, ester, or alkyl borane having the formula $R^2B(R^4)_2$, wherein R^2 is defined above, and R^4 is alkoxy, hydroxy, or alkyl borane;

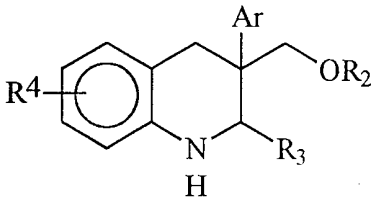
d) reacting each of the plurality of different 2-halo-3-alkoxy-alkenes with said boronic acid, ester, or alkyl borane and a suitable transition metal catalyst for a time sufficient to produce a plurality of different compounds of the formula (II), and



(II)

e) subjecting each of the plurality of products of the formula (II) to hydroboration amination to yield a plurality of different compounds of the formula (I).

25. A process for simultaneously preparing a plurality of different compounds of the formula (I):



(I)

where Ar is an aryl or heteroaryl group which can be substituted or unsubstituted; and

R^2 and R^3 are a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or heterocyclic rings;

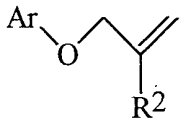
wherein said process comprises the steps of:

a) providing a plurality of different hydroxyaromatics having the general formula ArOH, wherein Ar is defined above;

b) reacting in solution each of the plurality of different hydroxyaromatics with a 2,3-dihaloalkene, so as to form a plurality of different of 2-halo-3-alkoxy-alkenes;

c) providing a boronic acid, ester, or alkyl borane having the formula $R^2B(R^4)_2$, wherein R^2 is defined above, and R^4 is alkoxy, hydroxy, or alkyl borane;

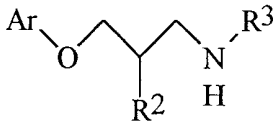
d) reacting each of the plurality of different 2-halo-3-alkoxy-alkenes with said boronic acid, ester, or alkyl borane and a suitable transition metal catalyst for a time sufficient to produce a plurality of different compounds of the formula (II), and



(II)

e) subjecting each of the plurality of products of the formula (II) to a three component hetero Diels Alder reaction to form a plurality of different compounds of the formula (I).

26. A process for simultaneously preparing a plurality of compounds of the formula (I):



(I)

where Ar is an aryl or heteroaryl group which can be substituted or unsubstituted; and

R^2 and R^3 are a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclic rings;

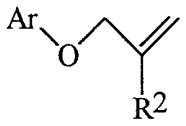
wherein said process comprises the steps of:

a) providing a plurality of different hydroxyaromatics having the general formula ArOH, wherein Ar is defined above;

b) reacting in solution each of the plurality of different hydroxyaromatics with a 2,3-dihaloalkene, so as to form a plurality of different of 2-halo-3-alkoxy-alkenes;

c) providing a boronic acid, ester, or alkyl borane having the formula $R^2B(R^4)_2$, wherein R_2 is defined above, and R^4 is alkoxy, hydroxy, or alkyl borane;

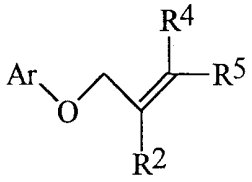
d) reacting each of the plurality of different 2-halo-3-alkoxy-alkenes with said boronic acid, ester, or alkyl borane and a suitable transition metal catalyst for a time sufficient to produce a plurality of different compounds of the formula (II), and



(II)

e) subjecting each of the plurality of products of the formula (II) to reductive cleavage to yield a plurality of different compounds of the formula (I).

27. A process for simultaneously preparing a plurality of different compounds of the formula (I):



(I)

where Ar is an aryl or heteroaryl group which can be substituted or unsubstituted; and

R^2 , R^4, R^5 are substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclic ring;

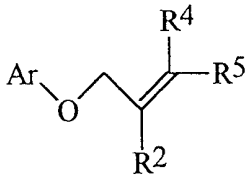
wherein said process comprises the steps of:

a) reacting in solution a hydroxyaromatic having the formula ArOH with a 2,3-dihaloalkene, wherein Ar is defined above, so as to form a 2-halo-3-alkoxy-alkene solution;

b) providing a plurality of different boronic acids, esters, or alkyl boranes, each having the general formula $R^2B(R^3)_2$, wherein R^2 is defined above and R^3 is an alkoxy, hydroxy, or alkyl group; and

c) reacting each of the plurality of different boronic acids, esters, or alkyl boranes with a portion of the 2-halo-3-alkoxy alkene solution and a suitable transition metal catalyst for a time sufficient to produce a plurality of different compounds of the formula (I).

28. A process for simultaneously preparing a plurality of different compounds of the formula (I):



(I)

where Ar is an aryl or heteroaryl group which can be substituted or unsubstituted; and

R^2, R^4, R^5 are substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclic rings;

wherein said process comprises the steps of:

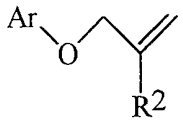
a) providing a plurality of different hydroxyaromatics having the general formula ArOH, wherein Ar is defined above;

b) reacting in solution each of the plurality of different hydroxyaromatics with a 2,3-dihaloalkene, so as to form a plurality of different of 2-halo-3-alkoxy-alkenes;

c) providing a boronic acid having the formula $R^2B(R^3)_2$, wherein R^2 is defined above and R^3 is alkoxy, hydroxy, or alkyl; and

d) reacting each of the plurality of different 2-halo-3-alkoxy-alkenes with said boronic acid, ester, or alkyl borane and a suitable transition metal catalyst for a time sufficient to produce a plurality of different compounds of the formula (I).

29. A reaction vessel on which a plurality of compounds are physically separated from each other, wherein the compounds are of the formula (I):



where Ar is aryl or heteroaryl; and

R^2 is a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclic ring .

30. The reaction vessel of claim 23, which is a wellplate apparatus.

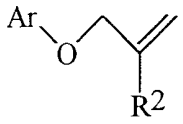
31. The reaction vessel of claim 23, which is a 96 well microtiter plate.

32. A method of optimizing the biological activity of a compound which comprises the steps of :

contacting a plurality of compounds physically separated from each other with an assay, and

determining if any of the plurality of compounds has biological activity,

wherein the plurality of different compounds are of the formula (I):



where Ar is hydroxyaromatic; and

R^2 is a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclic ring .

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12037

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07C 41/06; C07D 215/00, 215/12; B01L 3/00, 11/00

US CL :Please See Extra Sheet.

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. : 568/584, 585, 630, 631, 657; 546/152, 173; 422/101, 102; 702/19, 22

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 Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MIYAURA et al. Palladium-Catalyzed Reactions of Organoboron Compounds and Their Mechanism. Chemical Reviews. November 1995, Vol. 95, No. 7, pages 2460-2465.	1-28
A	KOBAYASHI et al. A New Methodology for Combinatorial Synthesis. Preparation of Diverse Quinoline Derivatives Using a Novel Polymer-Supported Scandium Catalyst. J. Am. Chem. Soc. September 1996, Vol. 118, No. 37, pages 8977-8978.	1-28
X	US 5,609,826 A (CARGILL et al) 11 March 1997, col. 4, line 58 to col. 5, line 7.	29-31
Y	US 5,691,137 A (ROSBASH et al) 25 November 1997, col. 1, line 49 to col. 3, line 15.	32

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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

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

"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)

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

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

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12037

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

568/584, 585, 630, 631, 657; 546/152, 173; 422/101, 102; 702/19, 22

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, CAS ONLINE, CASREACT
search terms: boronic acid, borane, dibromopropene, palladium tetrakis(triphenylphosphine), hydroboration, suzuki coupling, olefin, hydroboration amination