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(71) Demandeur/Applicant:
YLEKTRA INC., CA

(72) Inventeurs/Inventors:
LI, WEI, CA;
SIU, TUNG, CA;
YUDIN, ANDREI K., CA

(74) Agent: BLAKE, CASSELS & GRAYDON LLP

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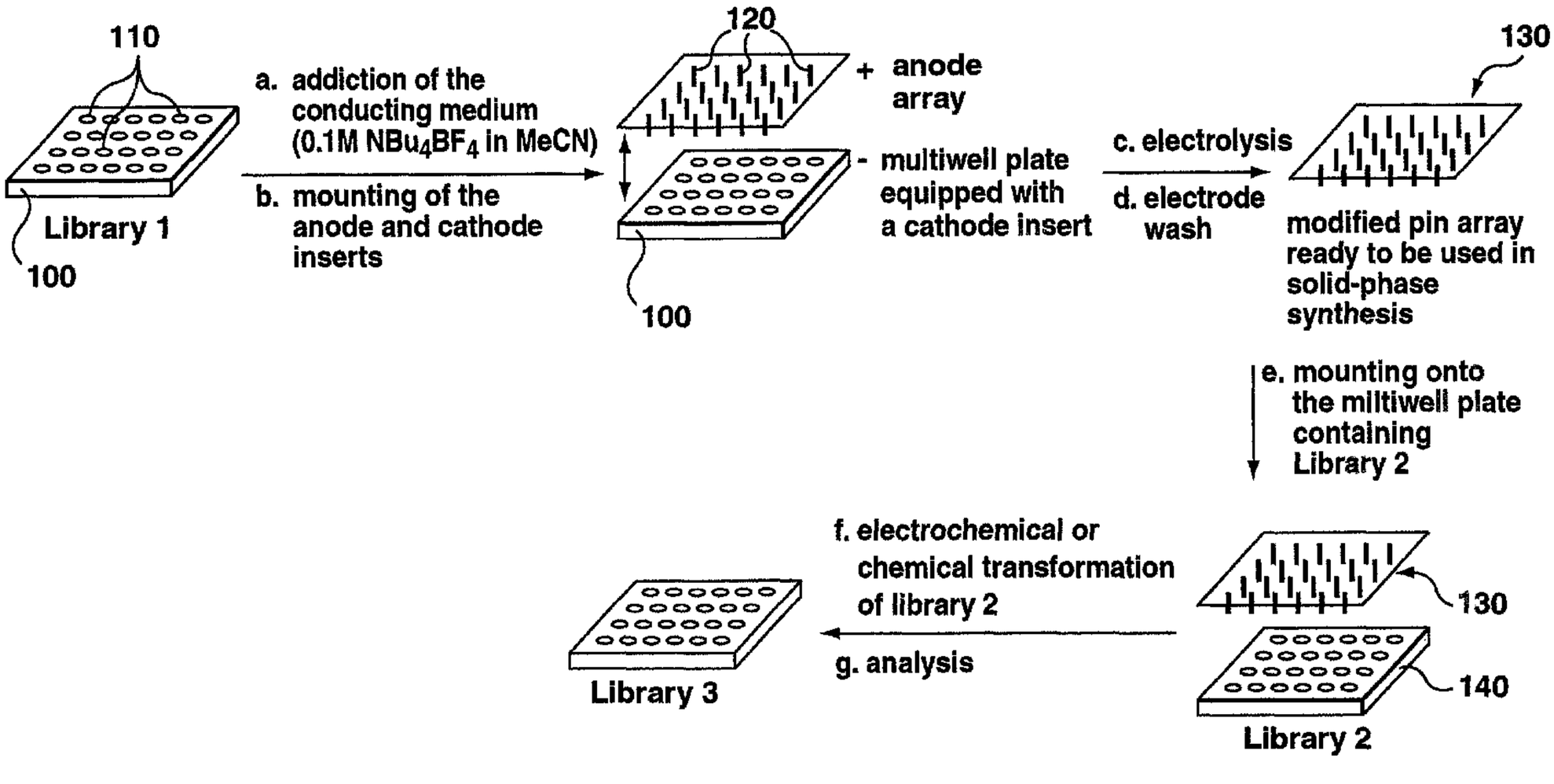
(54) Title: SPATIALLY ADDRESSABLE ELECTROLYSIS PLATFORM AND METHODS OF USE



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An electrochemical cell system and method are described. The electrochemical cell system provides a matrix of reaction cells (110) with a first electrode in each cell (110) and a single multiple element counter electrode (120, 130) wherein there is a separate element which is inserted into each cell (110). Methods and applications of the multiple electrode platform are described. Also described are modified electrodes having immobilized redox catalysts at the electrode surfaces and their use in optimizing performance in electrochemical processes.

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(71) Applicant *(for all designated States except US)*: **YLEKTRA INC.** [CA/CA]; 80 St. George Street, Toronto, Ontario M5S 3H6 (CA).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **YUDIN, Andrei, K.** [RU/CA]; 30 Humewood Drive, Toronto, Ontario M6C 2W4 (CA). **SIU, Tung** [CN/CA]; 730 Dovercourt Road, Toronto, Ontario M6H 2W9 (CA). **LI, Wei** [CN/CA]; 230 Oak Street, Apt. 1108, Toronto, Ontario M5A 2E2 (CA).

(74) Agent: **GRAY, Brian, W.**; Blake, Cassels & Graydon LLp, Box 25, Commerce Court West, Toronto, Ontario M5L 1A9 (CA).

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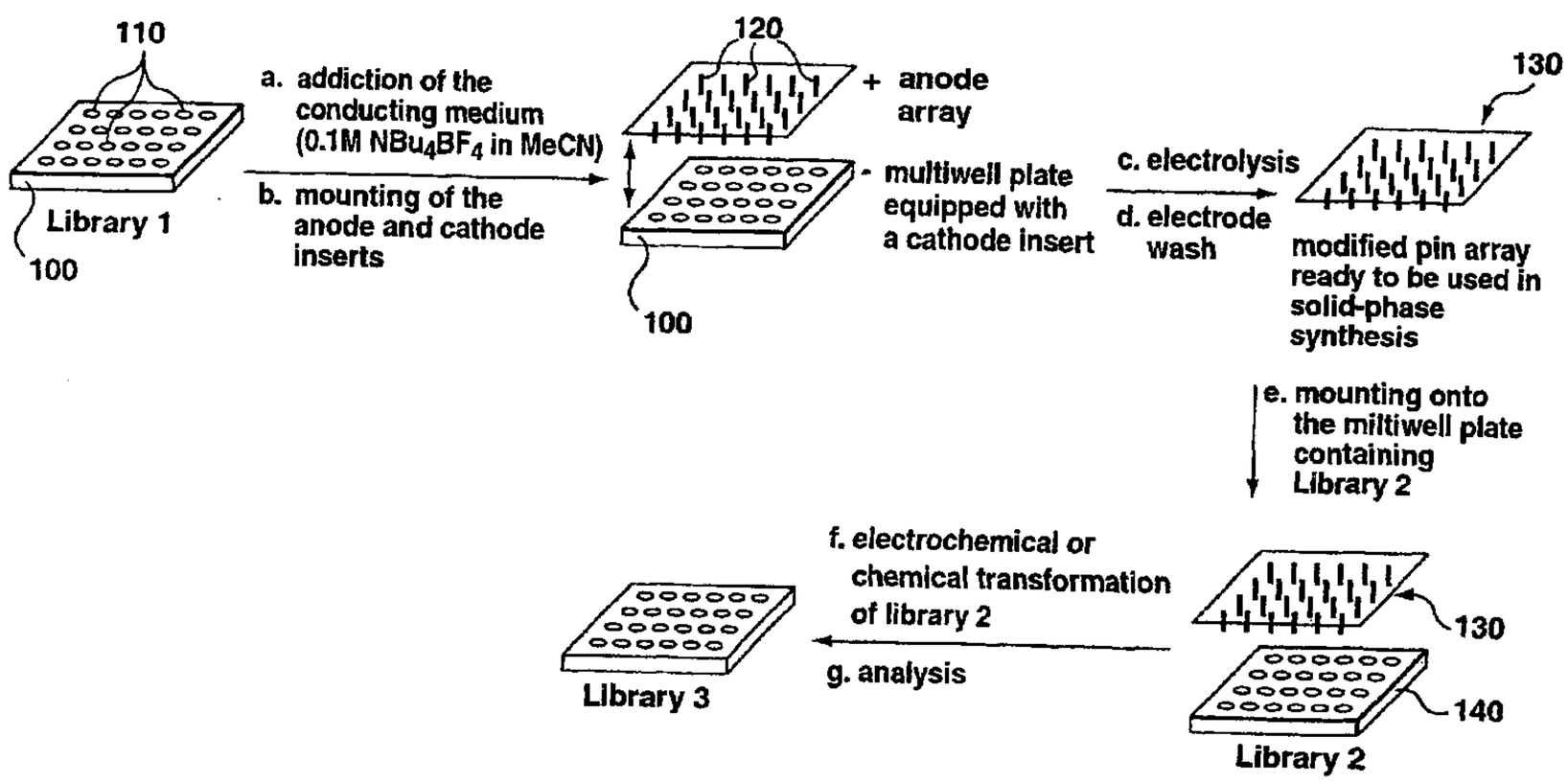

(57) Abstract: An electrochemical cell system and method are described. The electrochemical cell system provides a matrix of reaction cells (110) with a first electrode in each cell (110) and a single multiple element counter electrode (120, 130) wherein there is a separate element which is inserted into each cell (110). Methods and applications of the multiple electrode platform are described. Also described are modified electrodes having immobilized redox catalysts at the electrode surfaces and their use in optimizing performance in electrochemical processes.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Title: Spatially Addressable Electrolysis Platform and Methods of Use

FIELD OF THE INVENTION

The present invention is in the field of synthetic chemistry relating to combinatorial and high throughput chemical synthesis and is particularly concerned with an apparatus and method for combinatoral catalysis of chemical reactions and parallel synthesis.

BACKGROUND OF THE INVENTION

The demand for diverse compound libraries for screening in the drug discovery programs has been the major driving force behind development of new methodologies for high-throughput synthesis (Lam et al. (1991); Houghten et al. (1991); Fodor et al. (1991); Dewitt et al. (1993); Bunin et al. (1994)). Much emphasis has been placed on solid phase techniques due to facilitated separation of excess reagents and by-products from the resin-bound compounds. Solution phase approach, on the other hand, has the advantages of shorter reaction times and easier scale-up. Among solution phase techniques applied to parallel synthesis and combinatorial chemistry, electrosynthesis remains an area of tremendous, albeit underutilized, potential (Genders et al. (1996)). Considerable advances in creating molecular diversity not available by other means, and/or running known processes under mild conditions, would be possible if electrosynthesis was carried out in a high-throughput fashion.

A long-standing challenge in this area is to control the fate of electrogenerated intermediates. One possible solution is to mediate electron transfer by immobilizing a catalytically active species in the diffusion layer. Such immobilization can be accomplished *via* formation of catalyst-impregnated films at the electrode surface or *via* covalent linking of the corresponding catalyst precursors to the electrode surface (Figure 1). Precedents for these approaches exist and immobilization of electrocatalysts often results in increased catalyst lifetimes and higher turnover numbers compared to the corresponding homogeneous processes (Murray (1980); Deronzier and Moutet (1996)). Nonetheless, the field remains largely underdeveloped with the main difficulties being low faradaic efficiency, leaching of the surface-bound catalysts, and low current densities.

As just mentioned, the techniques of combinatorial chemistry (Ellman et la. (1995); Snapper et al. (1996)) and high throughput parallel synthesis (Burgess et al. (1996)) were shown to facilitate the development of new homogeneous catalysts. Combinatorial syntheses of magnetoresistive materials have been documented (Schultz et al. (1995)), as have parallel approaches to the screening of heterogeneous oxidation catalysts (Willson et al. (1996); Hill and Gall (1996)).

However, to date no effective technologies are available to allow for high throughput of electrosynthetic reactions and processes.

SUMMARY OF INVENTION

The present invention provides a spatially addressable multi-well electrode platform in order to perform electrosynthesis, electrocatalysis, as well as cyclic voltammetry (CV) measurements in a microtiter plate format. Each one of the reaction vessels in this novel piece of instrumentation comprises two parts: (a) miniwell equipped with a first electrode in the well, or cell and (b) complementary counterelectrode for insertion into the cell – one for each cell therby creating an electrode platform. The electrode platform becomes functional when mounted onto the miniwell array.

Accordingly, the present invention provides an apparatus for conducting multiple electrosynthetic reactions simultaneously comprising: two or more cells; an electrode in each of said cells; a counter electrode for each of said electrodes; and an energy source coupled to provide energy to each pair of electrode and counter electrodes. Preferably the energy source provides galvanostatic conditions in each cell, and the electrode and counter electrode are either unmodified or are coated with a conducting polymer, preferably the conducting polymer is selected from functionalized polypyrrole, polythiophene, and copolymers thereof and the electrode and counter electrode are made from graphite, platinum, or ito glass.

According to another embodiment, an apparatus according to the present invention is provided with miniwells in a plate format and an electrode, preferably the cathode is located at the bottom of the vessel and the counter electrode is located on a platform member.

According to another embodiment the present invention provides an apparatus for conducting multiple electrosynthetic reactions simultaneously comprising: 96 cells, preferably in a block made of teflon or glass; an anode electrode in each of said cells; a complementary cathode electrode attached

to a common terminal each of which is for insertion into each of said cells; and an energy source coupled to provide energy to each pair of cathode electrode and anode electrodes.

In another aspect of the present invention there is provided a method of conducting multiple electrochemical reactions to produce libraries of compounds simultaneously in a single apparatus. According to one embodiment of the invention the method comprises the steps of: adding an appropriate quantity of electrolyte solution to each cell of an apparatus according to the present invention; adding an appropriate quantity of a substrate to each cell; adding an appropriate quantity of a reaction compound to each vessel; placing the apparatus in a medium to maintain temperature; conducting electrolysis; and isolating and characterizing any reaction products. Preferably the energy source according to the method provides galvanostatic conditions in each cell. More preferably the electrode and counter electrode are coated with a conducting polymer, most preferably the conducting polymer is selected from functionalized polypyrrole, polythiophene, and copolymers thereof.

According to another method of the invention the electrode and counter electrode are made from graphite, platinum or ito glass, and the two or more cells are miniwells in a plate format. Preferably the electrode is located at the bottom of the vessel and the counter electrode is located on a platform member.

According to any of the methods of the invention, preferably the electrolyte solution is acetonitrile.

Accordingly, practicing the methods of the invention provide for high throughput screening of diversely modified electrode surfaces and in a preferred format may lead to the discovery of new electrocatalytic systems through rapid optimization of parameters such as film composition, thickness, porosity, conductivity, and effective catalyst loading. Further, practicing the methods of the invention provide for facilitated rapid synthesis of diverse organic compounds.

Other features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit

and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described in relation to the drawings in which:

Figure 1 (Prior Art) is a conceptual configuration of an electrode modified with an immobilized catalyst;

Figure 2 (a) illustrates 4x4 array of electrolysis cells as used in the Teflon block and glass vial embodiment of the invention before electrode assembly;

Figure 2 (b) illustrates the 4x4 array of Figure 2(a) after electrode assembly;

Figure 3 illustrates a 96 well "microtitre plate" configuration of an electrode platform of the present invention;

Figure 4(a) illustrates a polypyrrole film deposition on the surface of an electrode according to the present invention (X indicates a spacer of variable length and ML_n indicates a catalyst);

Figure 4(b) illustrates copolymerization of pyrroles of Figure 4A covalently attached to an oxidized surface of an electrode of the present invention (X indicates a spacer of variable length and ML_n indicates a catalyst);

Figure 5(a) illustrates solution-phase chemistry for the parallel synthesis of the 3-substituted pyrrole library;

Figure 5(b) illustrates polypyrrole surface modification. EDC: N-ethyl-N'-(dimethylaminopropyl)carbodiimide; NHS: N-hydroxysuccinimide; RNH_2: electrocatalyst precursor;

Figure 6 illustrates the current density effect on reaction between a carbamate and methanol;

Figure 7 illustrates the temperature effect on reaction between a carbamate and methanol;

Figure 8 illustrates the content effect of acetonitrile on reaction between a carbamate and methanol;

Figure 9 illustrates the yield of parallel electrolysis of a number of substrates in a number of alcohols;

Figure 10 illustrates a catalytic oxygen reduction service wherein (B* = B + Co(II); C* = C + Cu(I));

Figure 11 illustrates two examples of electrocatalytic surfaces (X: spacer of variable length; pPy: polypyrrole);

Figure 12 illustrates solution-phase chemistry of a reaction scheme for generating a library of substituted pyrroles;

Figure 13 illustrates an approach toward a library of PP/PT copolymer-based supports;

Figure 14 illustrates the solid phase synthesis of a library of reverse-turn peptidomimetics via two electrochemically controlled steps which are mixed with traditional chemical reactions: c. anodic oxidation; d. cathodic reduction; and

Figure 15 illustrates the general methodology for the preparation of a library of conducting supports and their subsequent use in solid-phase synthesis.

DETAILED DESCRIPTION OF THE INVENTION

Electrochemistry is at the interface of solution and solid-phase chemistry as the electron transfer steps take place in the Helmholtz double layer at the electrode surface. Highly reactive intermediates such as radical-ions, radicals, carbanions and carbocations can be generated under very mild reaction conditions in that region. Thus, many well established electrosynthetic reactions proceed with little or no by-products. In addition, these processes often lead to compounds that are not readily accessible using traditional methodologies. Selected examples include Kolbe electrolysis and electrohydrodimerization (EHD), which give carbon-carbon bond formation in a manner difficult to match by other routes (Utley (1994)). Another advantage of electrosynthesis over conventional chemical methods is selective transformation of functional groups by controlling the applied potential. For example, nitroalkanes can be selectively reduced to hydroxylamines or amines (Cyr et al. (1990)).

Electrochemical methods were introduced in the field of combinatorial chemistry only recently by Smotkin and Mallouk in parallel screening of electrocatalysts (Reddington et al. (1998)). In their study, a 645-member electrode array containing five elements and their binary, ternary and quaternary combinations, was screened in order to identify the most active alloy catalyst compositions for the electrooxidation of methanol. Protons generated at the anode were detected by a fluorescent acid-base indicator which was then correlated with catalytic activity. In the area of

synthetic applications, a handful of electrochemically generated solid supports and solid-phase electrochemical reactions appeared. For instance, the feasibility of running Merrifield chemistry on amino-derivatized polypyrrole support, prepared electrochemically, was demonstrated by Pickett et al. (Morlat-Therias et al. (1998)). Pilard and coworkers (Pilard et al. (1998); Marchand et al. (2000)) showed that the sulfonamide N-S linkage can be cleaved electrochemically with high selectivity on the surface of functionalized polythiophenes. To date however, the combination of electrosynthesis and parallel synthesis of small organic molecules has not been achieved.

As mentioned above, the present inventors have developed a spatially addressable electrolysis multiple cell apparatus. According to one embodiment the apparatus comprises a 16-well electrolysis platform. While two different types of electrolysis cells are described further here, it will be readily understood by those skilled in the art that the specific features described are not limiting and that there can be many variations to the invention of the apparatus. Such variations will be readily apparent to those skilled in the art. In one instance, a Teflon block with 16 wells drilled into it was used while in another a set of 16 glass vials was used. As illustrated in Figure 2, the spatially addressable electrolysis multiple cell apparatus 10 has 16 Teflon or cylindrical glass cells 20 arranged in a 4 by 4 array, each equipped with a tubular stainless-steel cathode 30 and a graphite rod anode 40. The stainless-steel cathodes were welded into a stainless-steel plate 50, which acts as a common terminal for the connection to a current source. The choice of graphite and stainless-steel for the anode and cathode is not limiting and as will be readily appreciated other materials may be used including carbon (felt, cloth, reticulated vitreous carbon, glassy carbon), platinum (rods, mesh foam), titanium (rods), ito glass, and mercury.

The graphite anodes served as working electrodes and were insulated from each other and cathodes by planting through a Teflon plate. Parallel connection of the 16 cells was achieved using this set-up.

According to a further embodiment there is provided a spatially addressable 96-well electrode platform in order to perform electrosynthesis as well as cyclic voltammetry (CV) measurements in a microtiter plate format (see Figure 3). In this respect a standard commercially available polypropylene plate may be used. Each one of the 96 reaction vessels in

this embodiment of instrumentation of the invention comprises two main elements: (a) a miniwell 60 equipped with a graphite (or other suitable material) electrode preferably at the bottom (not shown); and (b) complementary counter electrode 70 comprising graphite or other suitable material or platinum pierced through a polypropylene plate 80. The electrode platform becomes functional when this plate is mounted onto the miniwell array.

The electrical design illustrated was intended for running electrochemical reactions under galvanostatic (constant current) conditions. In theory, potentiostatic (constant potential) methods can be realized and as such are considered to be within the scope of the present invention. Such methods will require extra reference electrodes for each cell. By incorporating more sophisticated circuits well known to those skilled in the art, the parameter of each individual electrolysis cell can also be controlled, thereby allowing for optimized reaction conditions in each cell.

A DC power supply is used to run electrolyses under galvanostatic conditions and the total charge passed is determined by a digital coulometer. As is apparent to those skilled in the art, any other appropriate power supply may be used. When the parameters (solvent, supporting electrolyte, surface area of electrode, and temperature) are identical (or sufficiently equivalent) for each cell, the current, preferably, must be distributed evenly amongst all cells (e.g., 16, 96) and the individual cell current I_i is calculated from the total current I_t according to equation (1) (which is set out for a 16 well embodiment).

$$I_i = I_t/16,\ i = 1, 2, \ldots, 16 \qquad (1)$$

Electrode surface modification. As discussed, according to one embodiment of an apparatus of the invention, electrodes of the apparatus have immobilized redox catalysts at their surfaces. Polypyrrole film deposition *via* electropolymerization may be advantegeously used to attach catalysts to the electrode surfaces (Deronzier et al. (1996)) (see Figure 4(a)). Films of low adhesion are strengthened by copolymerization of pyrroles with monomers that are covalently attached to the oxidized surfaces (see Figure 4(b)). Catalyst precursors are immobilized at the anode or cathode, and are thereby transformed into transient redox-active species that will react with the corresponding substrates at the solid/liquid interface.

For example, using solution-phase chemistry a library of substituted pyrroles will be generated according to Figure 12. The length and nature of the spacer X is expected to influence conductivity and reagent permeability and constitutes a logical "point of diversity". A library of solid supports may be generated by anodic polymerization of the film precursor library on the electrode array of the SAEP.

Copolymerization chemistry of pyrrole and bithiophene based on the findings of van Dyke (van Dyke et al. (1991)). This access to diverse supports with controllable mass transport properties by *copolymerizing* different ratios of pyrrole and functionalized pyrrole or bithiophene. For example, Figure 13 features an approach toward a library of PP/PT copolymer-based supports. The pyrrole-based monomers will be prepared according to Figure 12. The high throughput screening of modified electrode surfaces using the SAEP format will lead to new solid supports through rapid optimization of parameters such as film composition, thickness, porosity, conductivity, and effective reagent loading. Surface characterization may be used on cyclic voltammetry and reflectance IR. The electrode platform may be regenerated upon polishing off the polymeric electrode modifiers.

In order to be suitable for a wide range of electrosynthetic applications, the materials preferably possess the highest conductivity in both cathodic *and* anodic regions. Figure 14 summarizes an illustrative experiment. It involves the solid phase synthesis of a library of reverse-turn peptidomimetics (Leznoff (1978)). Two electrochemically controlled steps are mixed with traditional chemical reactions in this example: c. anodic oxidation; d. cathodic reduction. Specifically, electrooxidative cyclization should provide the bicyclic lactam ring, whereas selective cleavage of the PP/PT-supported molecules will be based on the electroreductive scission of the sulfonamde bond (Pilard et al. (1998)).

Libraries of spatially addressable electrodes. A general methodology for the preparation of a library of conducting supports and their subsequent use in solid-phase synthesis is depicted in Figure 15. This methodology is not intended to be limiting, and other approaches will be readily apparent to those skilled in the art. Using solution-phase chemistry Library 1 of conducting support precursors is prepared. This step is followed by adding a conducting reaction medium into each well 110 in plate 100 and mounting

both the anode 120 and cathode inserts (not shown) onto the plate. Parallel electrolysis of the heterocyclic Library 1 will yield an array of modified pin electrodes 130. These are thoroughly washed and transferred onto a new plate 140 containing Library 2 which requires an electrosynthetic step for further elaboration into Library 3. At the support optimization step, each well could contain the same substrate - its electrochemical transformation is followed spectroscopically. According to this protocol it will become possible to select electrode modification chemistry with optimal performance in a given chemical or electrochemical library synthesis.

A Gilson 8x200 Pipetman may be used in small applications of the apparatus of the invention, however, to increase the throughput, a liquid handler (Gilson 215) for reaction layout, reagent dissolution and dispensing into J-KEM 96HC reaction blocks may be used. As will be appreciated, any liquid handler or reaction blocks may be used. The liquid-dispensing probe of the Gilson instrument has a liquid level sensing capability, essential to perform extractive work-ups. Solid phase extractions may be carried out using the IST VacMaster station and the Polyfiltronics hardware. A Gilson instrument may be integrated with Hewlett Packard 1100 LC/MS instrument or similar apparatus. The Savant DDA concentrator enables preparation of analytical samples and if necessary, allows for obtaining mass yields of individual library members.

The following non-limiting examples provide further illustrations of the present invention:

EXAMPLES

Examples 1-4 illustrate the α-alkoxylation of carbamates and sulfonamides (Nyberg et al. (1976); Edberson et al. (1979); Shono et la. (1984)). The process constitutes a direct and convenient method for generation and trapping of *N*-acyliminium cations. An alternative way of making the derivatized α-alkoxycarbamates is through the reduction of *N*-alkoxycarbonylactams (Nagasaka et la. (1986)). The latter method, however, requires cooling of the reaction mixture (-6°C) and relatively long reaction time (4 – 5 hours). The electrochemical method of the invention can essentially be performed at room temperature and typical reaction time is only 10 minutes for a reaction on a 1 mmol scale. The corresponding α-alkoxycarbamates are versatile synthetic intermediates and can be further elaborated into valuable products (Shono (1984)).

GENERAL METHODS AND MATERIALS FOR EXAMPLES 1-4

The electrolyte solution in each cell contained the substrate (0.5 M), tetrabutylammonium tetrafluoroborate ($Bu_4N^+BF_4^-$) as supporting electrolyte (0.05 M), tetralin as a GC internal standard, and 1:1 acetonitrile/alcohol as co-solvent in the case of substrate **1 – 5** (See Table 1 for compounds) or just acetonitrile in the case of substrate **6 – 11**. The SAEP was submerged in a water bath to maintain temperature at 30°C. Electrolysis proceeded at constant current until theoretical charge (2.0 F) had been passed through each cell. After electrolysis, approximately 0.2 mL of each solution was loaded onto a short plug of silica gel (0.5 cm i.d. x 5 cm) and eluted with ca. 5 mL of ethyl acetate/hexanes (1:1). The eluted solution was analyzed by GC (HP-5 capillary column, H2 carrier gas, 2.0 mL/min constant flow rate, temperature gradient 50 – 250°C, FID detector). In the case of sulfonamides **5**, the solvent was evaporated and the residue was flash chromatographed on silica gel column with 1:4 ethyl acetate/hexanes as eluent.

A solid phase extraction (SPE) procedure was tested on purification of product **10a** by following steps: 1) Conditioning an SPE column (*ISOLUTE*® C18, 0.5 g of sorbent) with 5 mL of MeOH (0.1 mL/sec). 2) Loading 0.2 mL of the reaction mixture (containing ca. 25 mg of product and supporting electrolyte) onto the column. 3) Column wash with 10 mL H_2O (0.1 mL/sec). 4) Elution column with 5mL MeOH (0.1 mL/sec) and eluent collection into a receiving test tube for GC analysis.

The NMR spectra were taken on Gemini 200 (200 MHz) with CDCl3 as solvent.

2-Propoxy-pyrrolidine-1-carboxylic acid *tert* butyl ester (Table 1, compound 1c): ^{1}Hd 0.92 (t, *J* = 7.2 Hz, 3H), 1.20-1.90 (m, 15H), 2.80-3.00 (m, 1H), 3.28 (t, *J* = 5.8 Hz, 2H), 3.80-4.00 (m, 1H), 5.25-5.50 (m, 1H).

2-Butoxy-pyrrolidine-1-carboxylic acid *tert* butyl ester (1d): ^{1}Hd 0.88 (t, *J* = 7.2 Hz, 3H), 1.32 (q, *J* = 8.1 Hz, 2H), 1.45-2.10 (m, 15H), 3.15-3.65 (m, 4H), 5.10-5.25 (m, 1H).

5-Methoxy-1-ethoxycarbonyl-L-proline methyl ester (2a): ^{1}Hd 1.10-1.40 (m, 3H), 1.70-2.50 (m, 4H), 3.30-3.50 (m, 3H), 3.70-3.80 (m, 3H), 4.00-4.25 (m, 2H), 4.30-4.45 (m, 1H), 5.15-5.40 (m, 1H).

5-Ethoxy-1-ethoxycarbonyl-L-proline methyl ester (2b): ^{1}Hd 1.15 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.3 Hz, 3H), 1.80-2.50 (m, 4H), 3.50-3.80 (m, 5H), 4.00-4.25 (m, 2H), 4.30-4.45 (m, 1H), 5.25-5.50 (m, 1H).

5-Propoxy-1-ethoxycarbonyl-L-proline methyl ester (2c): ^{1}Hd 0.89 (t, *J* = 7.2 Hz, 3H), 1.15-1.30 (m, 3H), 1.45-1.65 (m, 2H), 1.80-2.50 (m, 4H), 3.30-3.70 (m, 5H), 4.00-4.45 (m, 3H), 5.25-5.50 (m, 1H).

5-Butoxy-1-ethoxycarbonyl-L-proline methyl ester (2d): ^{1}Hd 0.90 (t, *J* = 7.2 Hz, 3H), 1.10-1.60 (m, 7H), 1.70-2.50 (m, 4H), 3.30-3.70 (m, 5H), 4.00-4.45 (m, 3H), 5.25-5.50 (m, 1H).

2-Butoxy-piperidine-1-carboxylic acid *tert* butyl ester (3d): ^{1}Hd 0.89 (t, *J* = 7.1 Hz, 3H), 1.10-1.90 (m, 17H), 2.80-3.00 (m, 1H), 3.20-3.60 (m, 4H), 3.80-3.95 (m, 1H), 5.25-5.50 (m, 1H).

2-Propoxy-piperidine-1-carboxylic acid ethyl ester (4c): ^{1}Hd 0.89 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.35-1.90 (m, 8H), 2.92 (t, *J* = 12.8 Hz, 1H). 3.28 (t, *J* = 5.7 Hz, 2H), 3.80-4.00 (b, 1H), 4.05-4.20 (m, 2H), 5.30-5.50 (b, 1H).

2-Methoxy-1-(toluene-4-sulfonyl)-piperidine (5a): ^{1}Hd 1.40-1.95 (m, 6H), 2.43 (s, 3H), 2.90-3.10 (m, 2H), 3.38 (s, 3H), 3.45-3.60 (m, 1H), 5.10-5.20 (b, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H).

1-Aza-6-oxabicyclo[5.4.0]undecan-2-one (6a): ^{1}H d 1.40-2.00 (m, 8H), 2.61 (ddd, J_1 = 14.3 Hz, J_2 = 6.2 Hz, J_3 = 2.9 Hz, 1H), 2.87 (ddd, J_1 = 14.6 Hz, J_2 = 11.6 Hz, J_3 = 3.6 Hz, 1H), 3.19 (qd, J_1 = 13.5 Hz, J_2 = 4.7 Hz, 1H), 3.74 (qd, J_1 = 11.7 Hz, J_2 = 3.1 Hz, 1H), 3.91 (dq, J_1 = 13.6 Hz, J_2 = 5.0 Hz, 1H), 4.06 (dq, J_1 = 12.2 Hz, J_2 = 3.8 Hz, 1H), 5.03 (q, *J* = 7.8 Hz, 1H); ^{13}C d 17.38, 22.73, 25.90, 29.79, 36.27, 38.53, 71.75, 85.45, 176.30. HRMS: 169.1104 (Calc. Mass 169.1103, $C_9H_{15}NO_2$).

1-Aza-4-methyl-5-oxabicyclo[4.4.0]decan-2-one (7a): ^{1}H d 1.28 (d, *J* = 6.4 Hz, 3H), 1.35-2.00 (m, 6H), 2.15-2.55 (m, 3H), 3.76-3.92 and 4.12-4.28 (two sets of multiplet, 1H), 4.52-4.78 (m, 2H); ^{13}C d 20.21, 21.47, 23.09, 23.89, 25.06, 25.26, 32.46, 33.32, 39.63, 40.30, 40.61, 41.63, 66.29, 70.01, 84.37, 86.74, 165.64, 166.78. HRMS: 169.1099 (Calc. Mass 169.1103, $C_9H_{15}NO_2$).

1-Aza-6-oxabicyclo[5.3.0]decan-2-one (8a): ^{1}H d 1.60-2.20 (m, 6H), 2.60-2.75 (m, 2H), 3.30-3.50 (m, 1H), 3.65 (td, J_1 = 12.1 Hz, J_2 = 2.3 Hz, 2H), 4.12 (dt, J_1 = 12.3 Hz, J_2 = 2.7 Hz, 1H), 5.09 (dd, J_1 = 5.8 Hz, J_2 = 2.5 Hz,

1H); ^{13}C d 22.44, 25.74, 34.45, 37.24, 73.11, 90.49, 175.01. HRMS: 155.0953 (Calc. Mass 155.0946, $C_8H_{13}NO_2$).

1-Aza-4-methyl-5-oxa-bicyclo[4.3.0]nonan-2-one (9a): ^1H d 1.10-1.30 (m, 5H), 2.95 (ddd, J_1 = 18.8 Hz, J_2 = 17.6 Hz, J_3 = 8.9 Hz, 2H), 3.20-3.40 (m, 2H), 3.80-4.00 (m, 1H), 4.05-4.25 (m, 2H), 4.87 + 5.06 (two sets of triplet, J = 5.7 Hz, 1H); ^{13}C d 17.76, 19.98, 22.02, 23.10, 32.45, 34.15, 45.86, 45.94, 64.63, 64.80, 69.06, 72.55, 83.81, 89.27, 174.24, 176.16. HRMS: 155.0950 (Calc. Mass 155.0946, $C_8H_{13}NO_2$).

1-Aza-6,9-dioxabicyclo[5.4.0]undecan-2-one (10a): ^1H d 1.60-2.20 (m, 2H), 2.58 (ddd, J_1 = 14.4 Hz, J_2 = 6.0 Hz, J_3 = 2.6 Hz, 1H), 2.75-2.90 (m, 1H), 3.20-3.40 (m, 1H), 3.56 (td, J_1 = 11.4 Hz, J_2 = 4.3 Hz, 1H), 3.65-4.10 (m, 5H), 4.08 (dt, $J1$ = 12.1 Hz, $J2$ = 4.0 Hz, 1H), 4.87 (t, J = 3.6 Hz, 1H); ^{13}C d 25.55, 35.68, 38.80, 65.93, 68.44, 72.22, 83.02, 176.39. HRMS: 171.0888 (Calc. Mass 171.0895, $C_8H_{13}NO_3$).

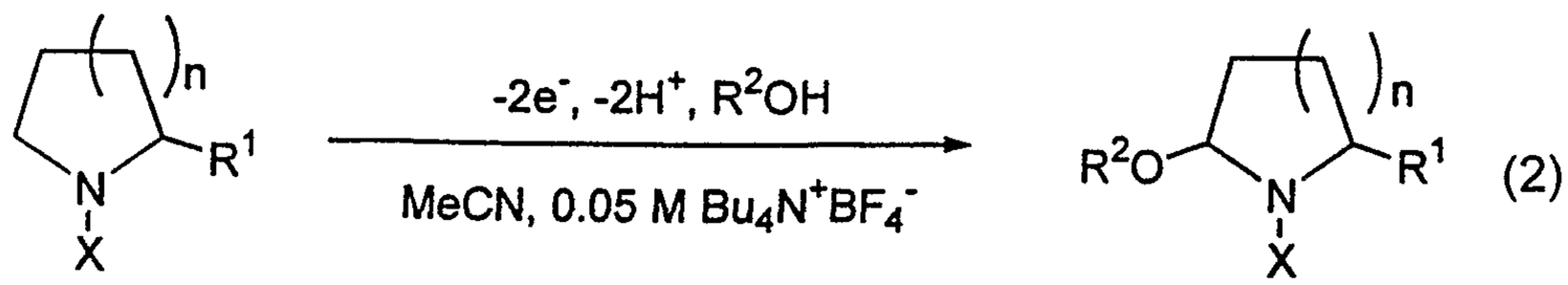
1-Aza-4-methyl-5,8-dioxabicyclo[4.4.0]decan-2-one (11a): ^1H d 1.29 (d, J = 6.2 Hz, 3H), 2.84 (td, J_1 = 13.3 Hz, J_2 = 3.4 Hz, 1H), 3.18 (dd, J_1 = 11.1 Hz, J_2 = 9.2 Hz, 1H), 3.35-3.50 (m, 2H), 3.85-4.05 (m, 4H), 4.46 (dd, J_1 = 14.0 Hz, J_2 = 2.0 Hz, 1H), 4.77 (dd, J_1 = 9.2 Hz, J_2 = 3.7 Hz, 1H); ^{13}C d 21.39, 39.74, 40.32, 67.24, 70.09, 70.47, 82.91, 166.11. HRMS: 171.0892 (Calc. Mass 171.0895, $C_8H_{13}NO_3$).

EXAMPLE 1

Using a 16 well embodiment of the apparatus, 16 reactions between carbamate **3** and *n*-propanol were conducted. The same GC yield of the alkoxylation product was obtained for each cell indicating that each one of them was operating under identical conditions. The individual cell current was calculated using equation (1).

EXAMPLE 2

A series of primary alcohols with acetonitrile as a co-solvent was then used, in a series of reactions with carbamates and sulfonamides according to equation (2) (carbamate where X=C, sulfonamide where X=S)



(2)

In order to find optimal electrolysis reaction conditions, the reaction between **3** and methanol was chosen. A current density of 80 mA/cm^2 and a temperature of 30°C were found to afford the highest yield and selectivity. Acetonitrile content was also optimized and a 50:50 (by volume) acetonitrile/alcohol mixture was found to give the highest conversion. The optimization results are shown in Figures 6 – 8. The supporting electrolyte was removed before GC analysis by passing the reaction mixture through a short plug of silica gel, which was eluted with ethyl acetate/hexanes (1:1). The solid phase extraction (SPE) technique was also applied at the product isolation stage (see experimental section).

EXAMPLE 3

Parallel electrosynthesis results for the substrates **1 – 4** and four alcohols are shown in Figure 9. In the cases of methanol and ethanol, all four substrates gave high yields, while small amounts of di-substituted by-products (up to 5%) were detected for substrates **1**, **3**, and **4**. No such by-products were found in the cases of *n*-propanol and *n*-butanol, which gave only moderate yields. We infer that the increase of chain length in alcohols is unfavorable for attacking the intermediate *N*-acyliminium cation for steric reasons.

EXAMPLE 4

The substrate **2** gave equal amounts of two diastereomeric products. The alkoxylation of sulfonamide **5** and intramolecular cyclization of substrates **6 – 11**, that led to the isolation of a series of hetero-bicyclic compounds, have also been conducted and the yields are given in Table 1. These alkoxylated derivatives can be easily transformed into valuable amidoalkylation productions, as shown by Shono (Shono (1984)).

EXAMPLES 5-7

Surface electrocatalysis with Immobilized Catalysts

The rate-limiting step in surface electrocatalysis is the reaction between immobilized catalysts and dissolved substrates (Anson (1980)). The efficiency of a given system, therefore, largely depends on film porosity that modulates the mass transport in the diffusion layer. It is preferable to incorporate Keggin-type heteropolyanion salts (Girault et al. (1987)) within the film during electropolymerization. Subsequent washing of the surface

leaves correspondingly sized domains (Aizawa et al. (1986)). Catalyst loadings are controlled by copolymerization of varied ratios of substituted and unsubstituted pyrroles. Preferably, optimization centers on the catalytic performance of the electrogenerated "combinatorial polymers" (Menger et al. (1995); Menger (1997)).

EXAMPLE 5

Figure 10 illustrates the use of polypyrrole-based films for the catalytic reduction of oxygen to H_2O, a process of great commercial value in the development of fuel cells. In a preferred approach, three pyrrole-containing monomers A, B, and C (Figure 10) are anodically polymerized to give a film composed of randomly sequenced polymer chains. It is expected that, upon complexation of the Cu(I) and Co(II) ions, certain segments of these polymers (e.g., the ACB unit) possess catalytic activity for the four electron reduction of oxygen to H_2O, emulating the active site of cytochrome c (Collman et al. (1997)). This is tested by changing the A/B/C monomer ratio, the nature of the R_1 and R_2 substituents of the cyclam monomer B, and the length of the spacer X. The turnover numbers (oxygen uptake) are then correlated with the occurrence of statistically formed "active sites".

EXAMPLE 6

Investigation of the catalytic activity of polypyrrole-bound transition metal complexes in atom and group transfer reactions is possible with an apparatus of the present invention. In contrast to combinatorial oxygen reduction surfaces (*vide supra*) that depend on the random assembly of the "active sites", these catalysts may be prepared by the electropolymerization of well-defined libraries of catalyst precursors made using solution-phase parallel synthesis in a one-compound-per-well format. For example, an epoxidation surface based on novel amino acid-derived catalysts (Figure 11(a)) may be used to explore cathodic activation of molecular oxygen. The use of manganese porphyrins as well as Schiff-base complexes in olefin epoxidation with oxygen has been documented (Murray et al. (1990); Horwitz et al. (1990)). It is possible to screen 1st row transition metals for catalytic activity. Manipulation of the diverse amino acid substituents on ligands during library preparation enables probing the enantioselectivity of oxygen atom transfer to prochiral substrates.

EXAMPLE 7

Using an apparatus of the invention, polymeric transition metal catalysts for the non-thermal activation of CO_2 at atmospheric pressure may be developed. Recent studies have documented the use of homogeneous Ni and Cr catalysts for the formation of carbonates from epoxides and CO_2 (Tascedda et al. (1995); Kruper et al. (1995)). Using a cyclam-based surface, the kinetic resolution of epoxides with cathodically activated CO_2 (see Figure 11(b)) at potentials where reduction to CO is inhibited may be investigated. A cyclam ligand library may be derived from chiral tetraamine precursors, pyrrole-containing diesters, and 1st row transition metal salts. As in the epoxidation example, "assay" for the catalytic activity of a given film will follow the electropolymerization step.

The apparatus of the present invention will enable the performance of parallel synthesis of film precursor libraries, electropolymerization of diverse monomers, characterization of the resulting films, and investigation of the films' catalytic activities in a variety of redox processes and has application in the following, non-limiting areas of chemistry:

1. Reduction of carbon-carbon double bonds
   - 1.1 Hydrodimerization of olefins
   - 1.2 Cathodic reduction of aromatics to 1,4-dihydro compounds
   - 1.3 Anodic addition to nucleophiles to olefins
2. Reduction of carbonyl groups
   - 2.1 Reduction of ketones and aldehydes to alcohols and hydrocarbons
   - 2.2 Reductive amination of ketones and aldehydes
   - 2.3 Reduction of carboxylic acids to aldehydes and alcohols
   - 2.4 Reduction of carboxamides to amines
   - 2.5 Reduction of esters to alcohols
   - 2.6 Reductive coupling of aldehydes and ketones with olefins
3. Reduction of aliphatic and aromatic nitrile and nitro groups to amines and hydroxylamines
4. Reductive coupling of imines, ketones, and aldehydes, and enol ethers.
5. Reductive cleavage of the O-O, S-S, C-C, C-S, C-N, and C-O bonds
6. Oxidation of hydrocarbons
   - 6.1 Oxidation of polynuclear aliphatic and aromatic hydrocarbons

6.2 Oxidation of methyl aromatics
6.3 Oxygenation of olefins
6.4 Epoxidation, dihydroxylation, aziridination, and aminohydroxylation of olefins
6.5 Oxidation of vinyl and allyl arenes for the formation of benzaldehydes and aryl ketones
7. Decarboxylation of carboxylic acids
8. Oxidative coupling
8.1 Oxidative coupling of esters
8.2 Oxidative coupling of phenols
9. Electrochemical fluorination
10. Mediated oxidation or reduction
10.1 Use of S-S, Se-Se, and Te-Te functionalities for indirect electroreduction
10.2 Metal-catalyzed C-C, C-O, C-N and C-S bond formation
11. Reduction of alkyl, aryl, acyl, and vinyl hanlides
11.1 Reductive coupling of alkyl halides with aldehydes and ketones
11.2 Reduction of acyl halides to aldehydes
11.3 Silylation of alkyl, aryl, acyl, and vinyl halides
12. Hydrogenation of heterocycles
13. Synthesis of electrogenerated reagents
14. Methoxylation of aromatic compounds and heterocycles
15. Sacrificial electrode-based processes
16. Formation of heterocyclic compounds
17. Synthesis of natural products

While the present invention has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the invention is not limited to the disclosed examples. To the contrary, the invention is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

Table 1

Table 1. α-Alkoxylation of Carbamates **1** – **4** and Sulfonamide **5** and Intramolecular Cyclization of **6** - **11**.

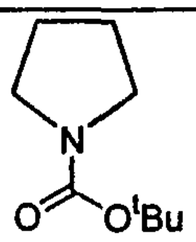
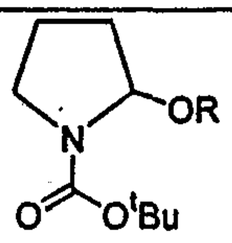
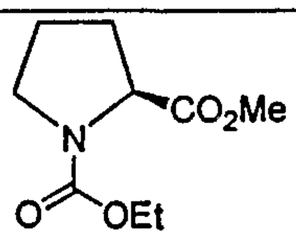
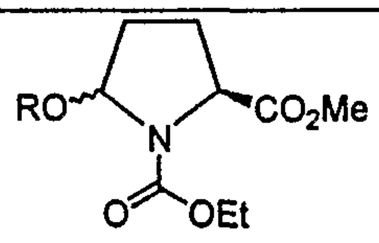
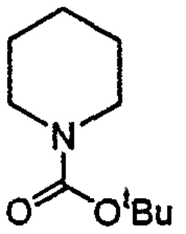
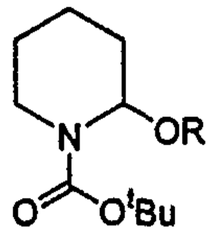
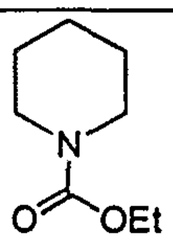
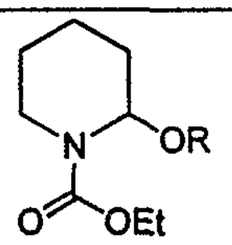
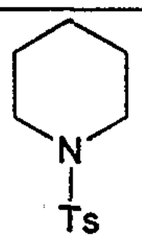
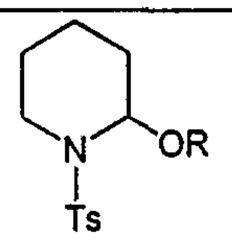
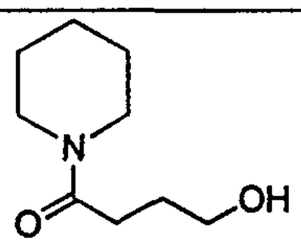
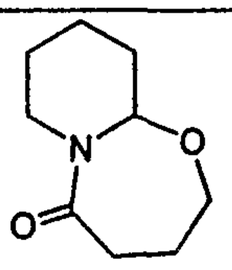
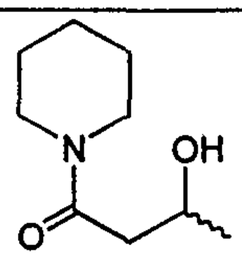
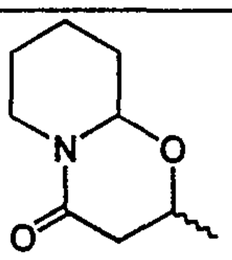
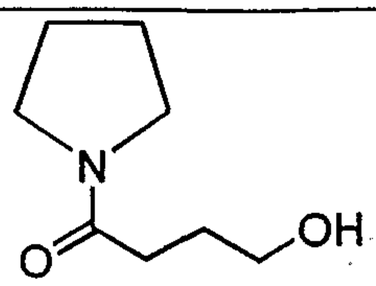
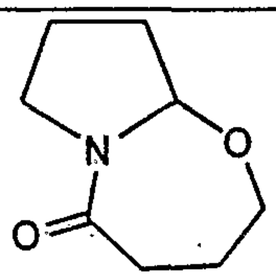
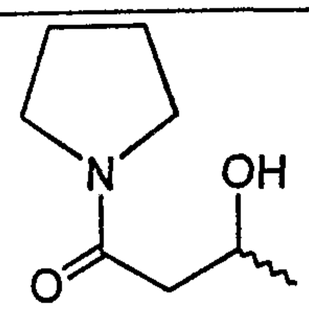
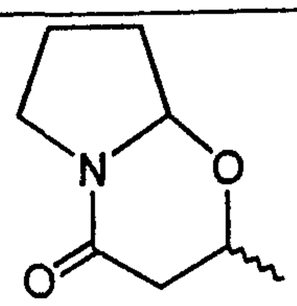
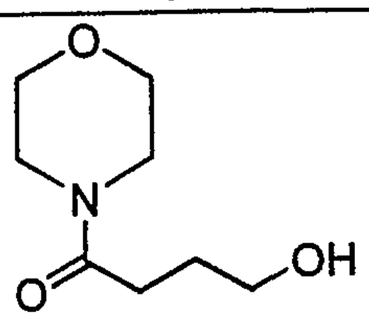
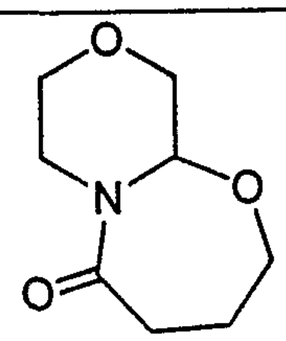
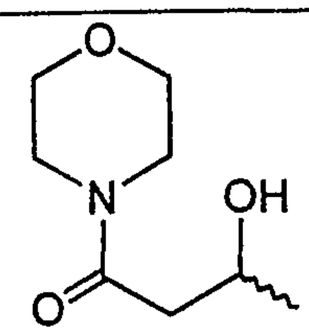
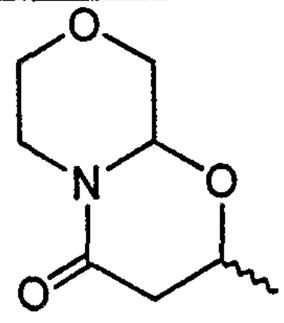
Substrate	Product	R	Yield, %
 **1**	 **1a – 1d**	**a**: Me **b**: Et **c**: ^{n}Pr **d**: ^{n}Bu	95 93 87 (75[a]) 80 (70[a])
 **2**	 **2a – 2d**	**a**: Me **b**: Et **c**: ^{n}Pr **d**: ^{n}Bu	92 (88[a]) 90 (88[a]) 86 (79[a]) 78 (72[a])
 **3**	 **3a – 3e**	**a**: Me **b**: Et **c**: ^{n}Pr **d**: ^{n}Bu **e**: ^{i}Pr	90 87 78 61 (60[a]) 63
 **4**	 **4a – 4d**	**a**: Me **b**: Et **c**: ^{n}Pr **d**: ^{n}Bu	91 89 85 (81[a]) 62
 **5**	 **5a – 5d**	**a**: Me **b**: Et **c**: ^{n}Pr **d**: ^{n}Bu	90[a] 85[a] 78[a] 60[a]
 **6**	 **6a**		80
 **7**	 **7a**		93
 **8**	 **8a**		94

Table 1 (continued)

 **9**	 **9a**		92
 **10**	 **10a**		95
 **11**	 **11a**		91

[a] Isolated yield.

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WE CLAIM:

1. An apparatus for conducting multiple electrosynthetic reactions simultaneously comprising:
   i) two or more cells;
   ii) an electrode in each of said cells;
   iii) a counter electrode for each of said electrodes; and
   iv) an energy source coupled to provide energy to each pair of electrode and counter electrodes.

2. An apparatus according to claim 1 wherein the energy source provides galvanostatic conditions in each cell.

3. An apparatus according to either of claims 1 or 2 wherein the electrode and counter electrode are coated with a conducting polymer.

4. An apparatus according to claim 3 wherein the conducting polymer is functionalized polypyrrole, polythiophene, or a functionalized copolymer of polypyrrole or polythiophene.

5. An apparatus according to anyone of claims 1-4 wherein the electrode and counter electrode are made from graphite, platinum, or ito glass.

6. An apparatus according to anyone of claims 1 to 5 wherein the two or more cells are miniwells in a plate format.

7. An apparatus according to claim 6 wherein the electrode is located at the bottom of the cell and the counter electrode is located on a platform member.

8. An apparatus for conducting multiple electrosynthetic reactions simultaneously comprising:
   v) 96 cells in a teflon block;
   vi) an anode electrode in each of said cells;

vii) a complementary cathode electrode attached to a common terminal each of which is for insertion into each of said cells; and

viii) an energy source coupled to provide energy to each pair of cathode electrode and anode electrodes.

9. A method of conducting multiple electrochemical reactions to produce libraries of compounds simultaneously in a single apparatus said method comprising the steps of:

i) adding an appropriate quantity of electrolyte solution to each cell of an apparatus according to claim 1;

ii) adding an appropriate quantity of a substrate to each cell;

iii) adding an appropriate quantity of a reaction compound to each cell;

iv) placing the apparatus in a medium to maintain temperature;

v) conducting electrolysis; and

vi) isolating and characterizing any reaction products.

10. A method according to claim 9 wherein the energy source provides galvanostatic conditions in each cell.

11. A method according to either of claims 9 or 10 wherein the electrode and counter electrode are coated with a conducting polymer.

12. A method according to claim 11 wherein the conducting polymer is functionalized polypyrrole, polythiophene, or a functionalized copolymer of polypyrrole or polythiophene.

13. A method according to anyone of claims 9-12 wherein the electrode and counter electrode are made from graphite, platinum or ito glass.

14. A method according to anyone of claims 9 to 13 wherein the two or more cells are miniwells in a plate format.

15. A method according to claim 14 wherein the electrode is located at the bottom of the cell and the counter electrode is located on a platform member.

16. A method according to anyone of claims 9 to 15 wherein the electrolyte solution is acetonitrile.

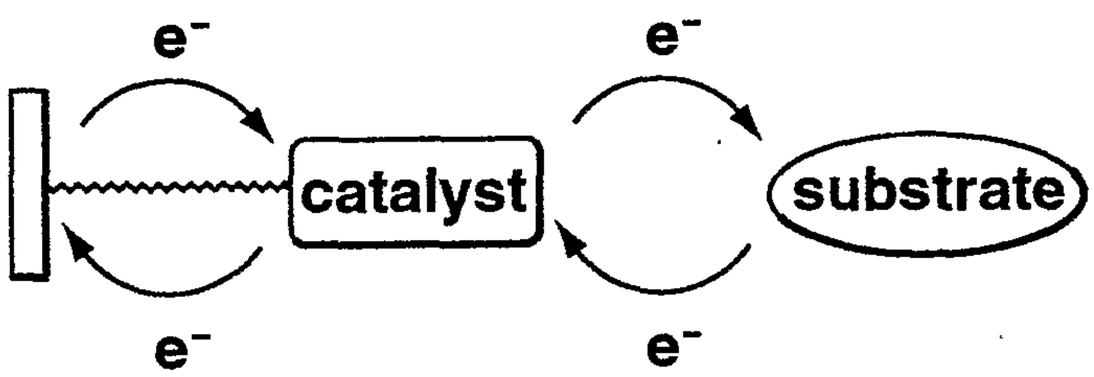


FIG. 1

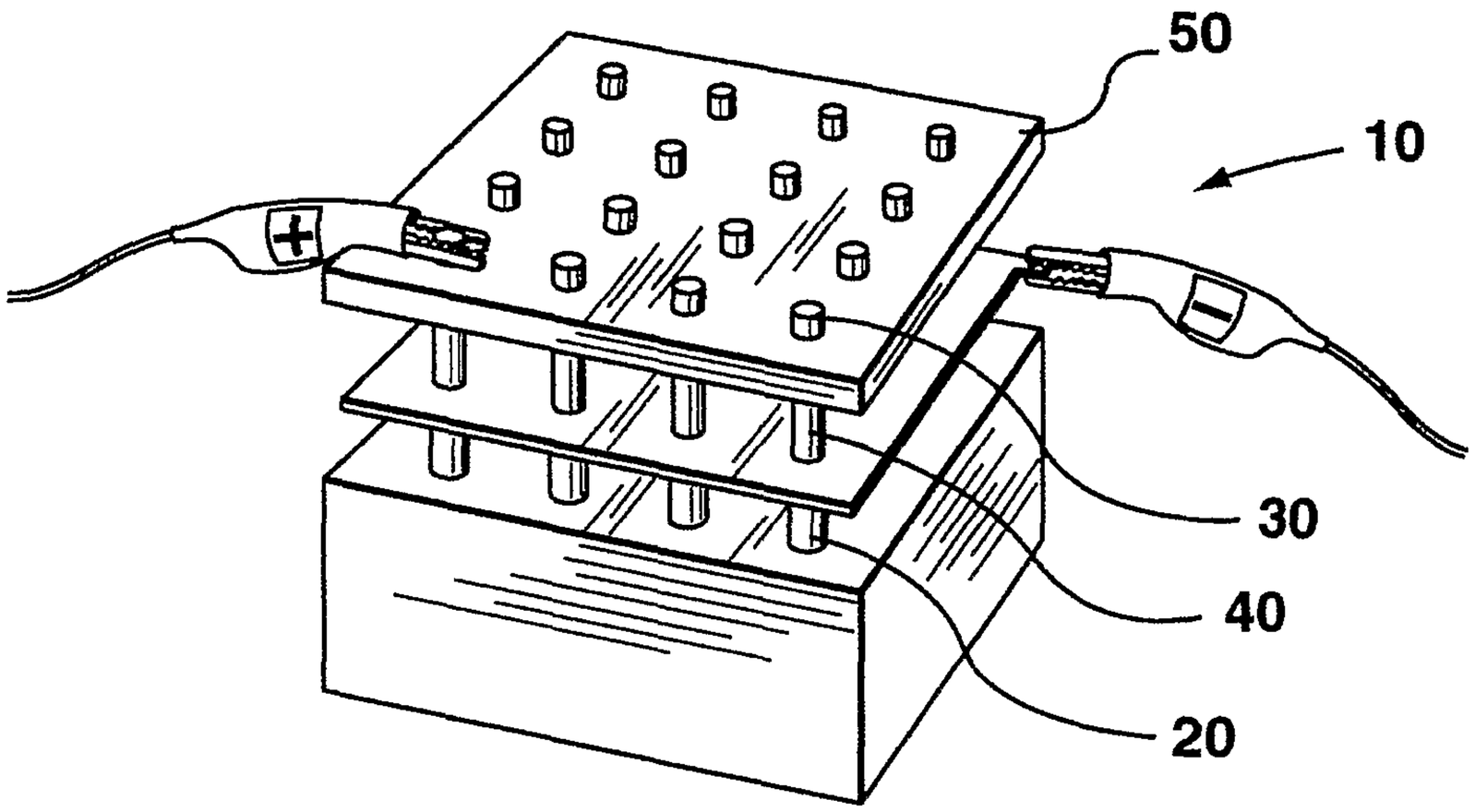


FIG. 2a

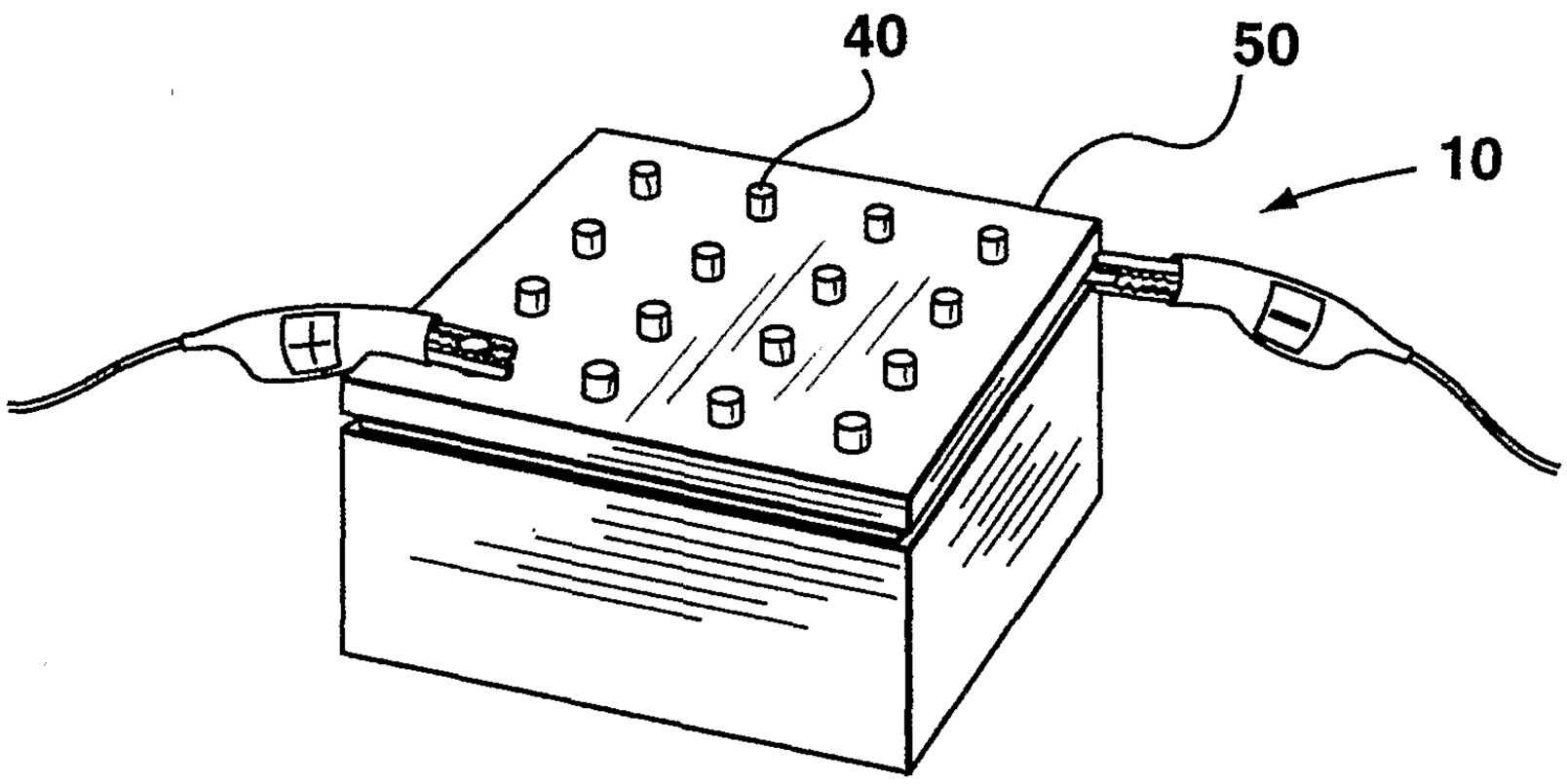


FIG. 2b

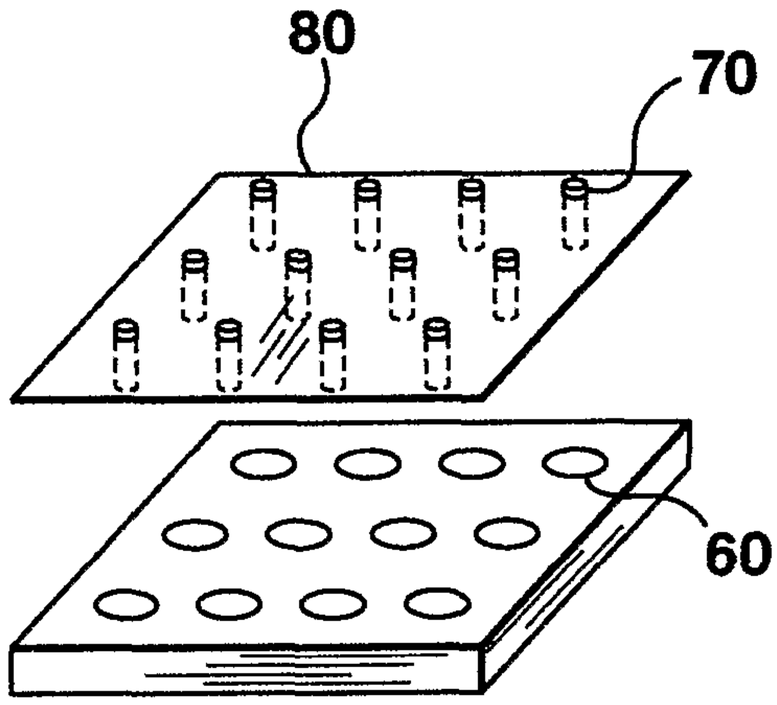


FIG. 3

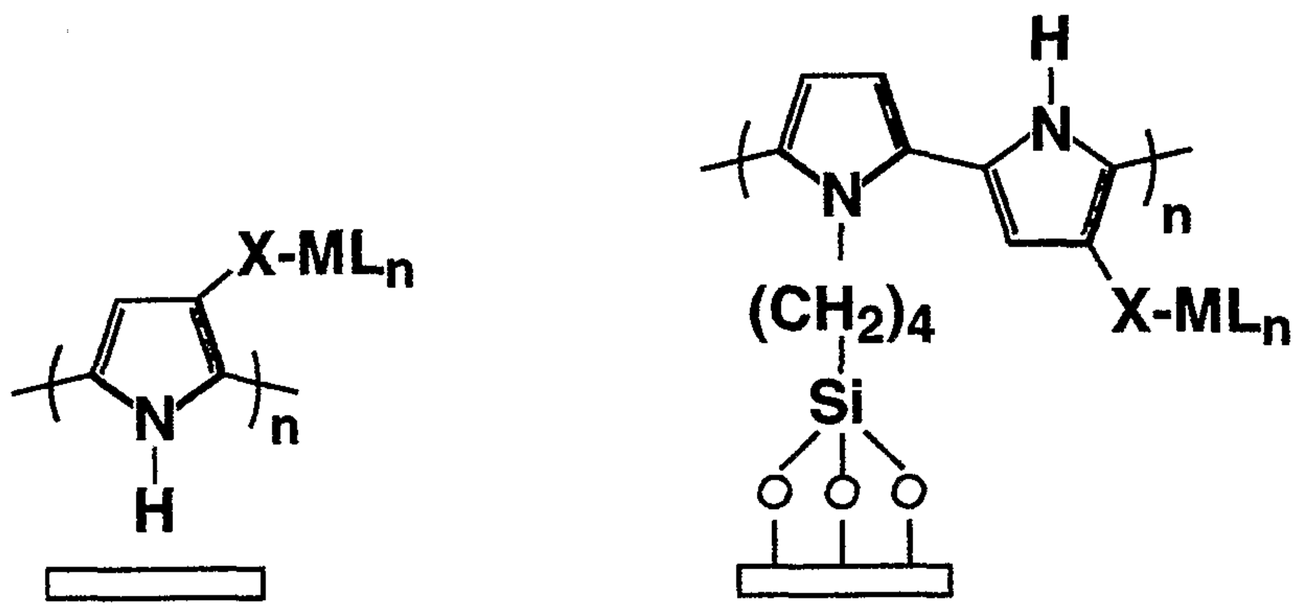


FIG. 4

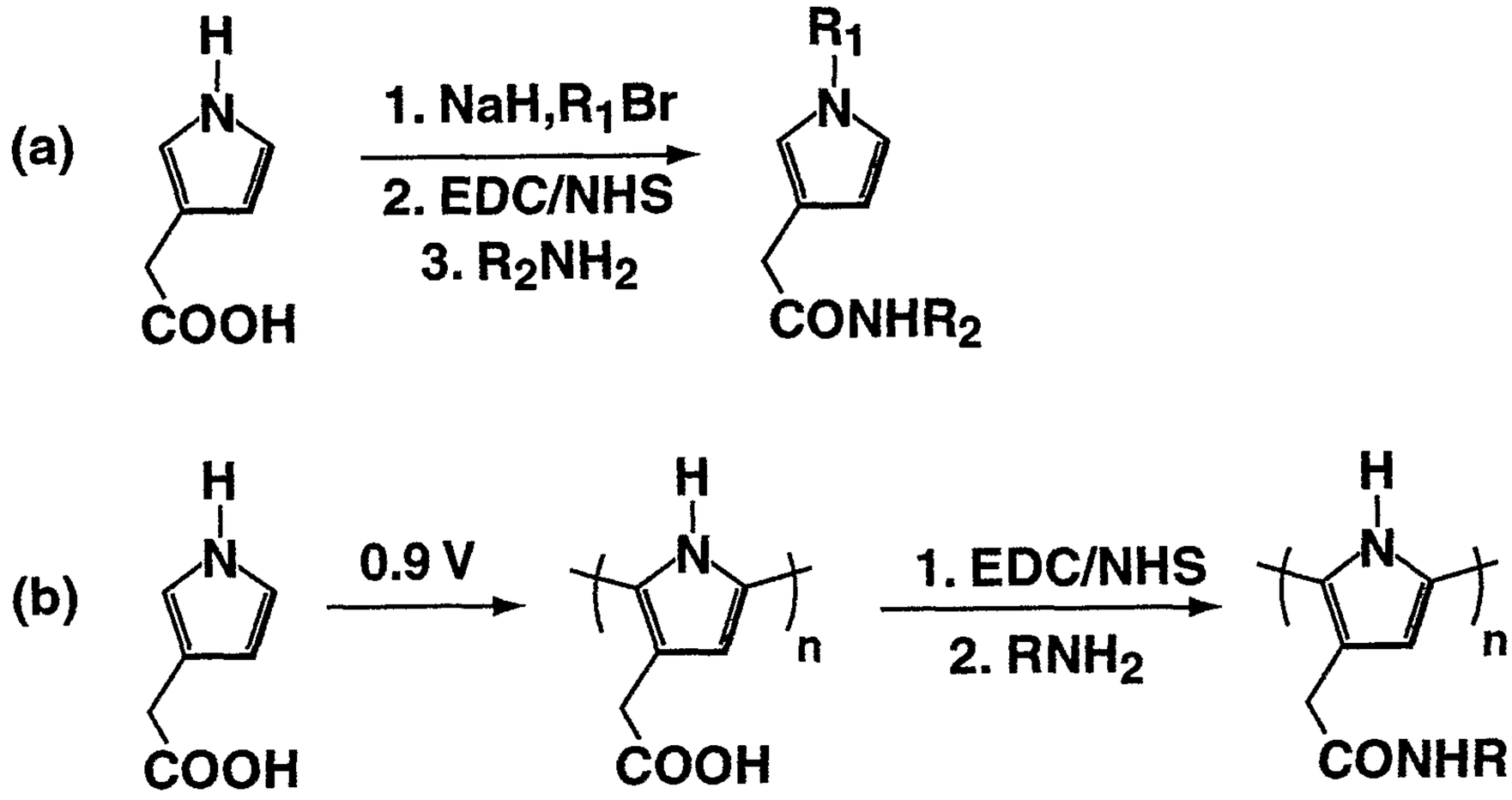
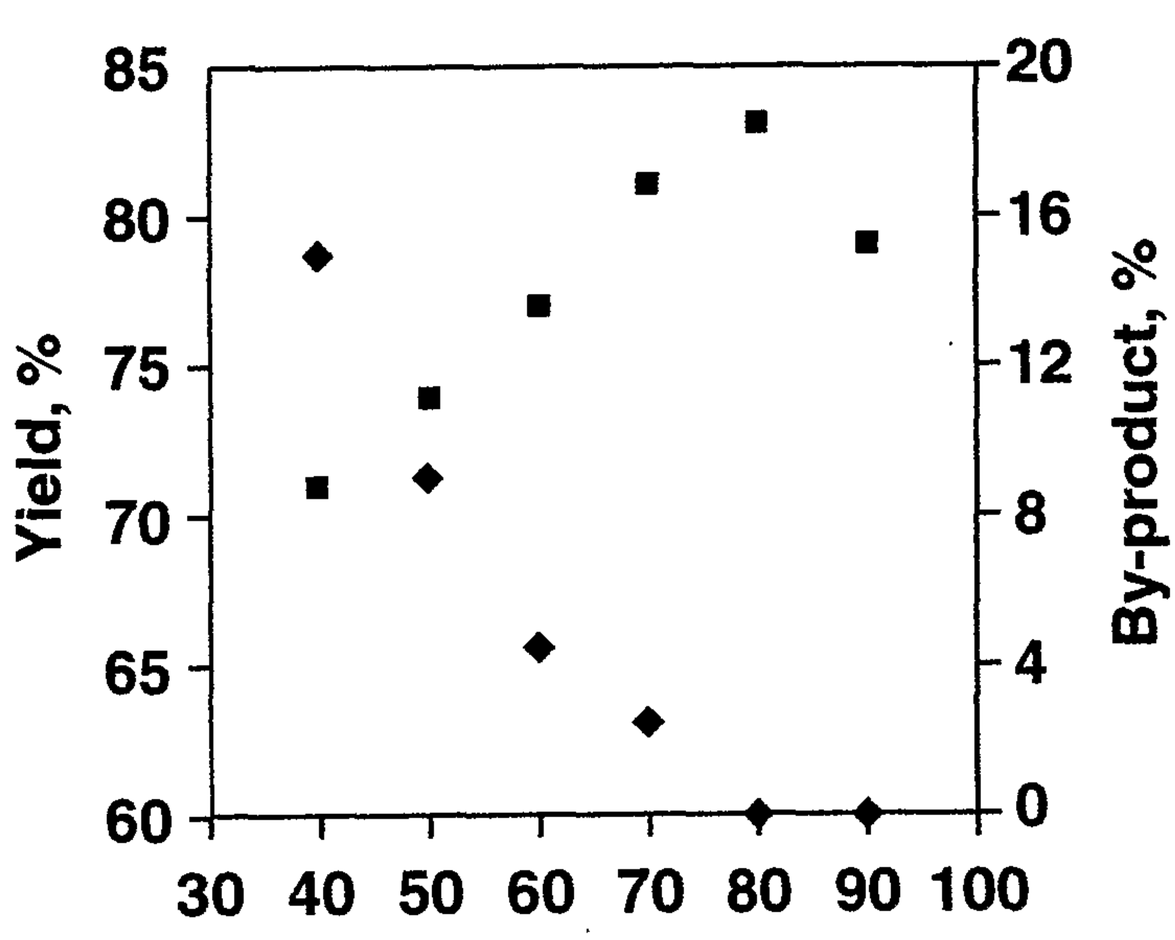

(a)
H
N
COOH
1. NaH,R1Br
2. EDC/NHS
3. R2NH2
R1
N
CONHR2
(b)
H
N
COOH
0.9 V
H
N
n
COOH
1. EDC/NHS
2. RNH2
H
N
n
CONHR

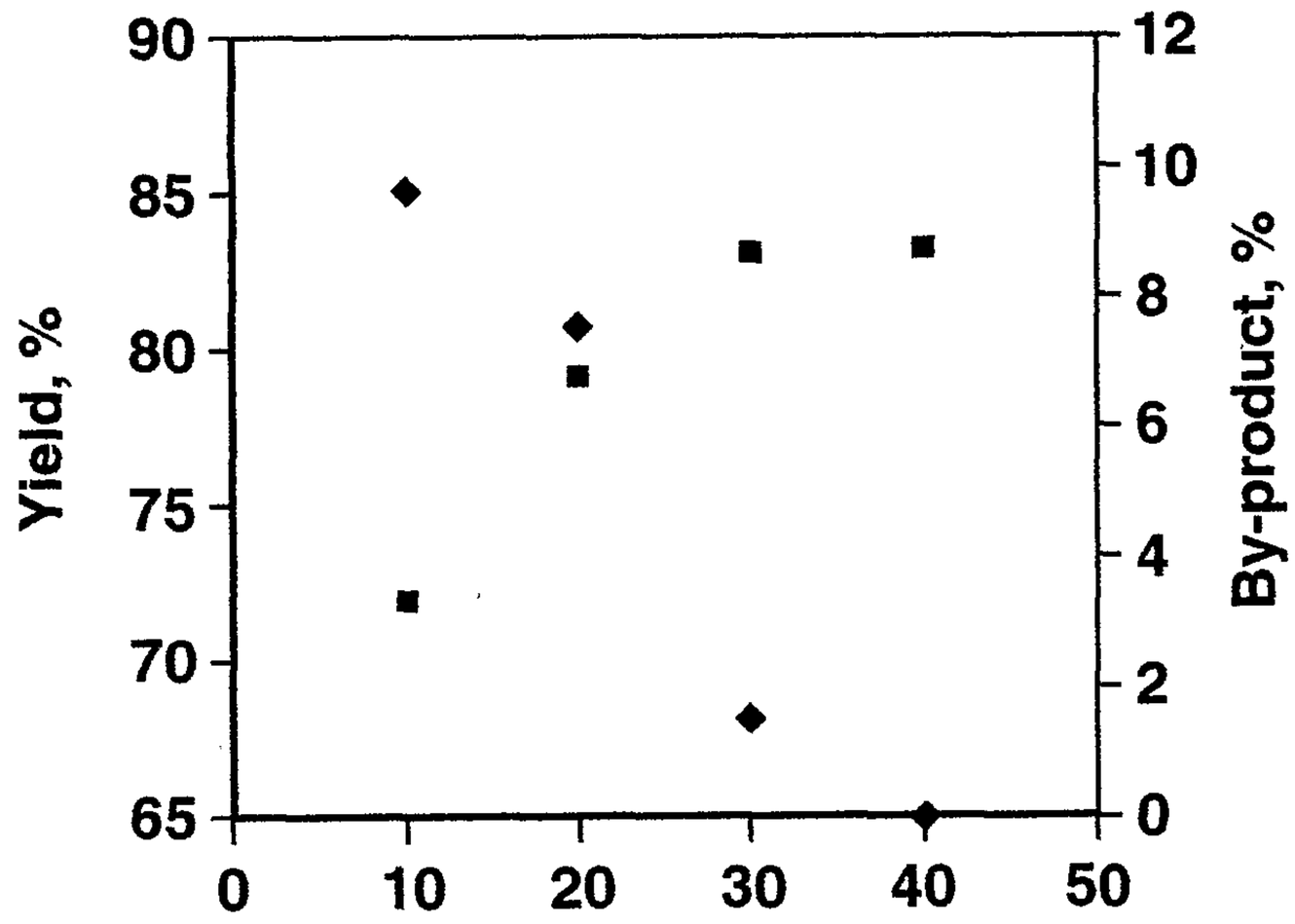
FIG. 5



Current density effect on reaction between 3 and methanol.

■:product; ♦ :disubstituted by-product.

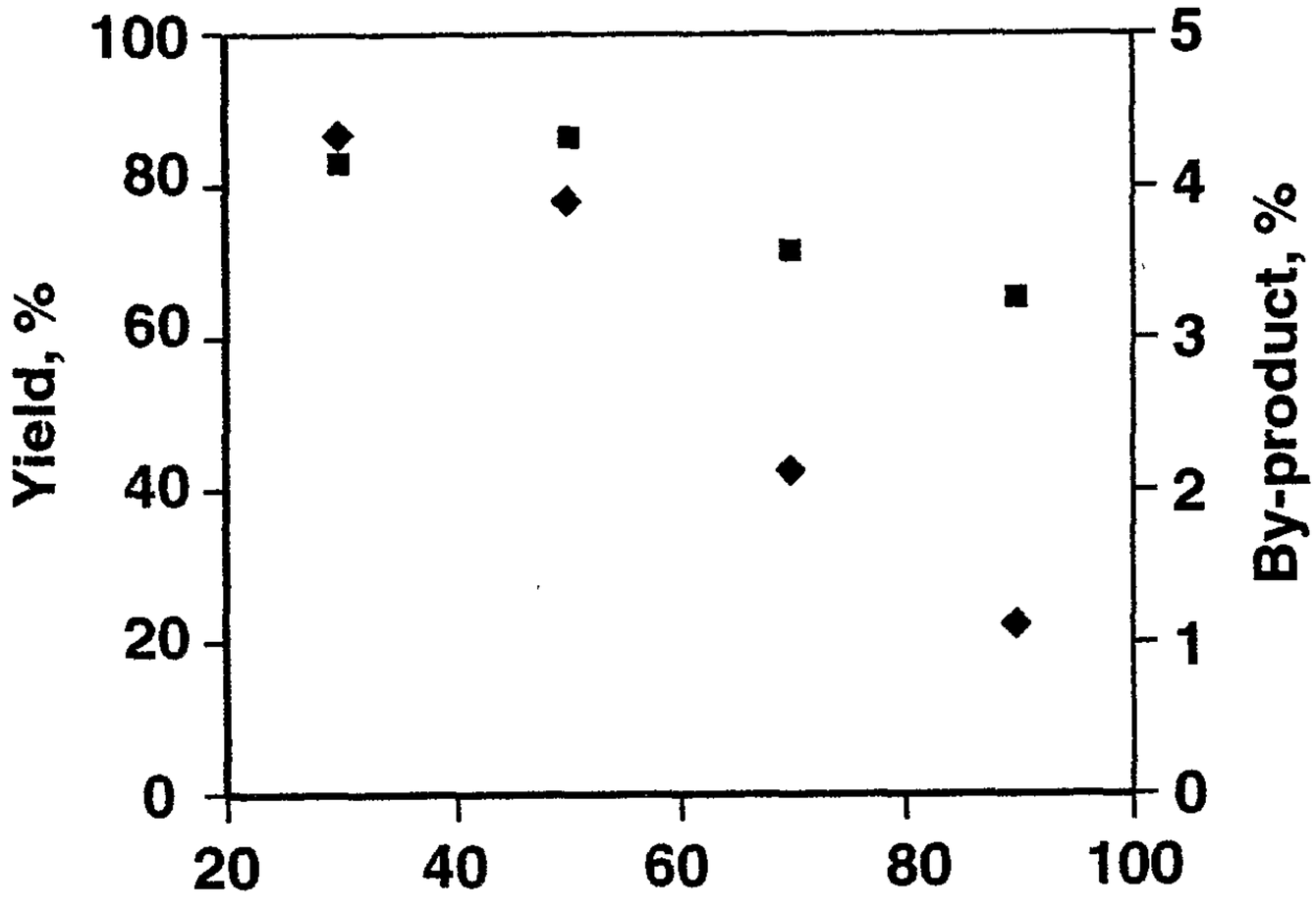
FIG. 6



Temperature effect on reaction between 3 and methanol.

■:product; ♦ :disubstituted by-product.

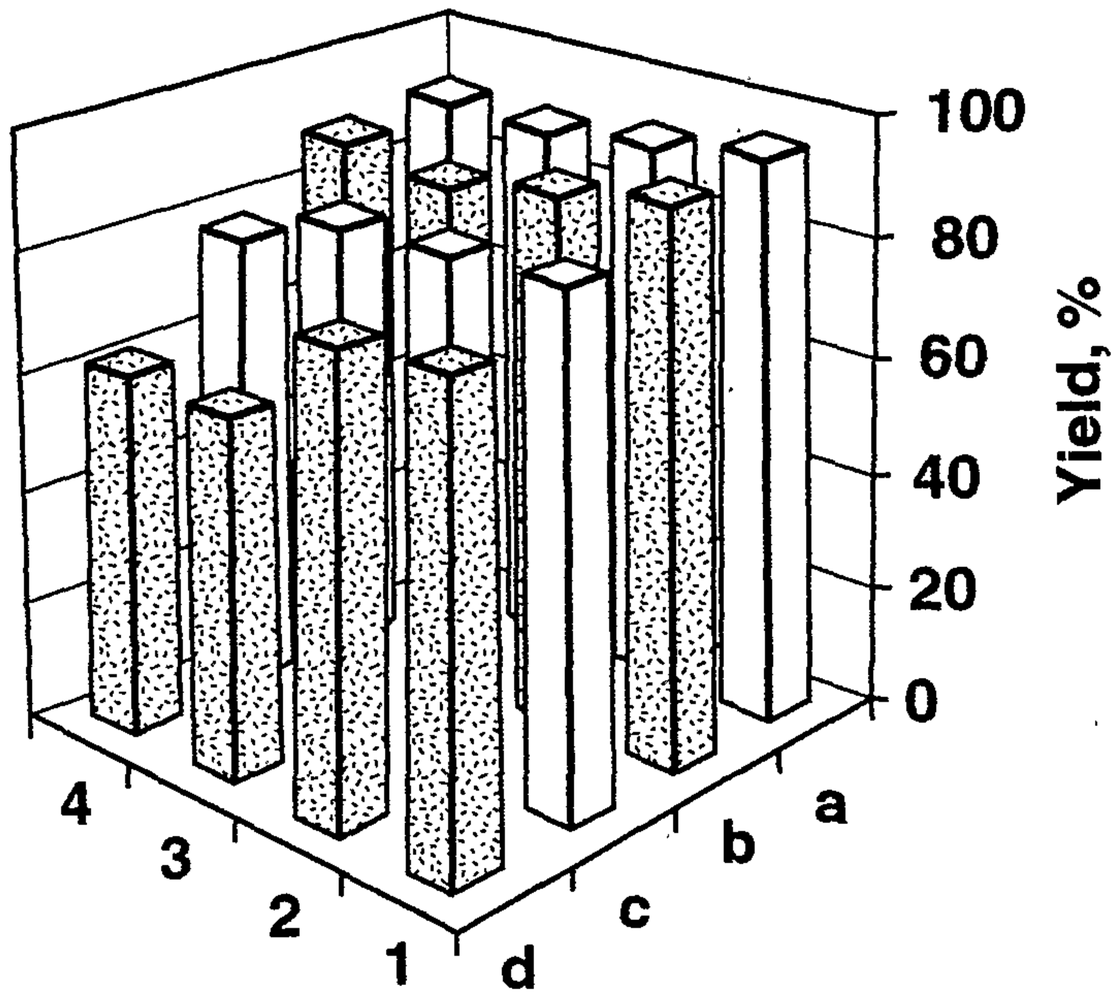
FIG. 7



Acetonitrile content effect on reaction between 3 and methanol.

■:product; ♦ :disubstituted by-product.

FIG. 8



Parallel electrolysis of substrate 1-4 in alcohols a-d

FIG. 9

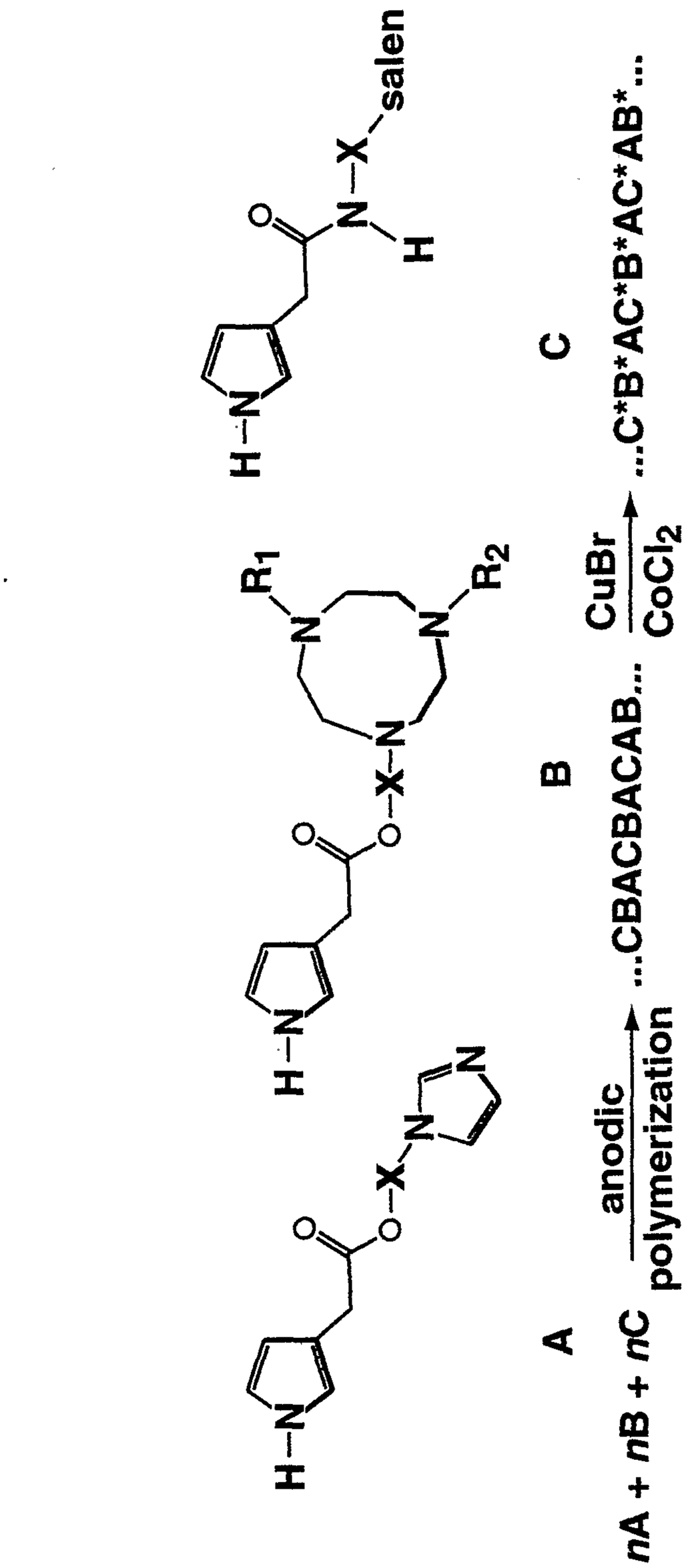
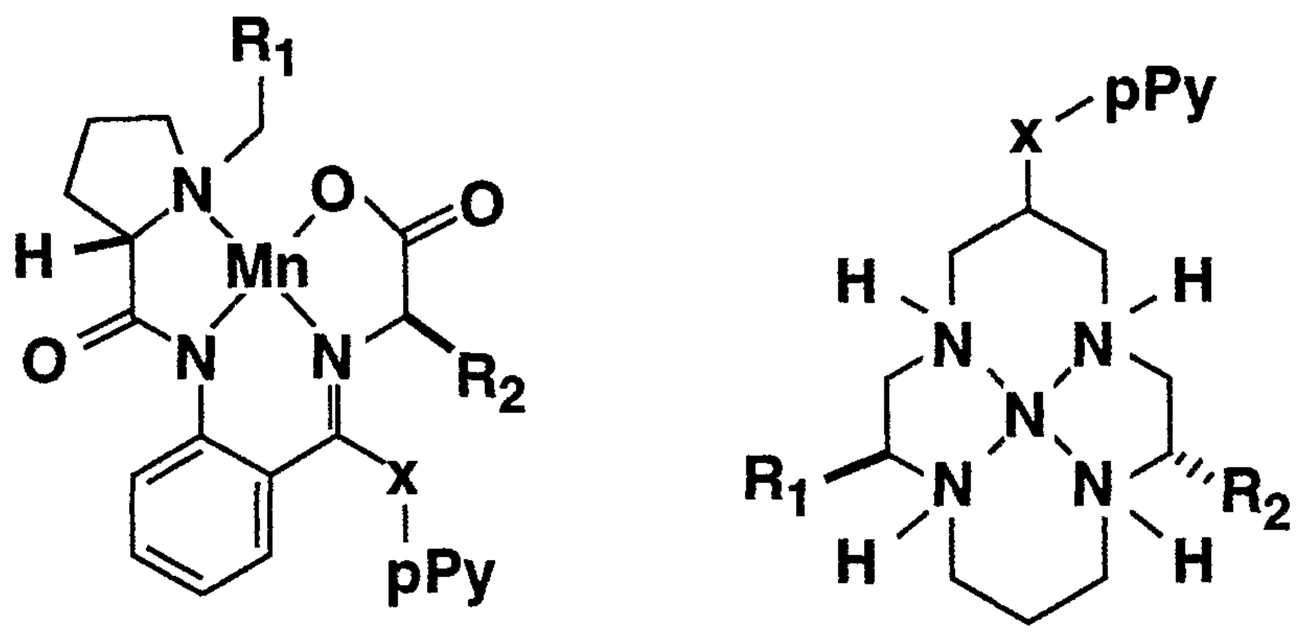

A
nA + nB + nC
anodic polymerization
...CBACBACAB...
B
CuBr
CoCl2
...C*B*AC*B*AC*AB*...
C
H
N
X
O
R1
R2

FIG. 10



(a) (b)

FIG. 11

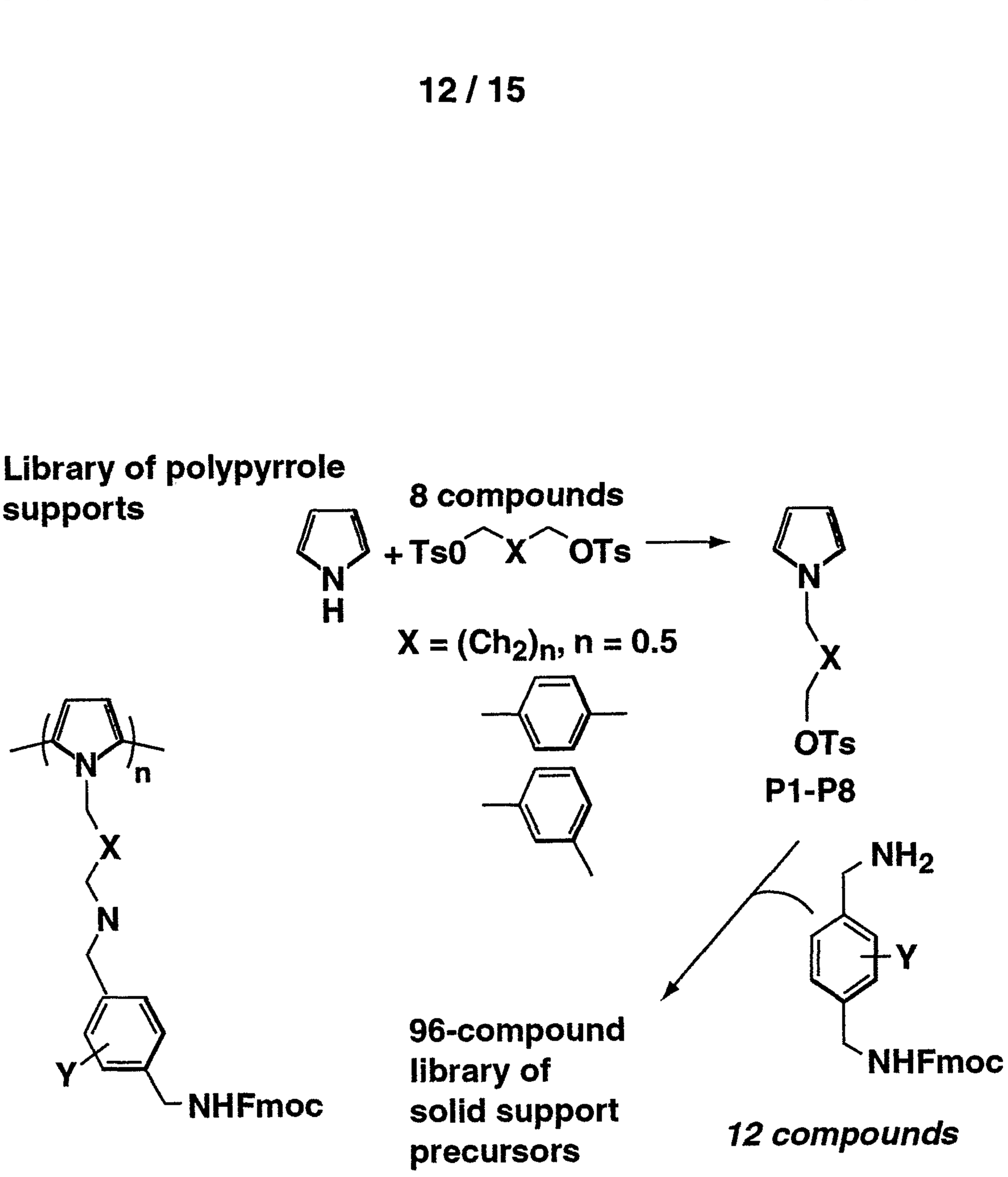

Library of polypyrrole supports
8 compounds
+ Ts0 X OTs
N
H
X = (Ch2)n, n = 0.5
N
X
OTs
P1-P8
N
n
X
N
Y
NHFmoc
96-compound library of solid support precursors
NH2
Y
NHFmoc
12 compounds

FIG. 12

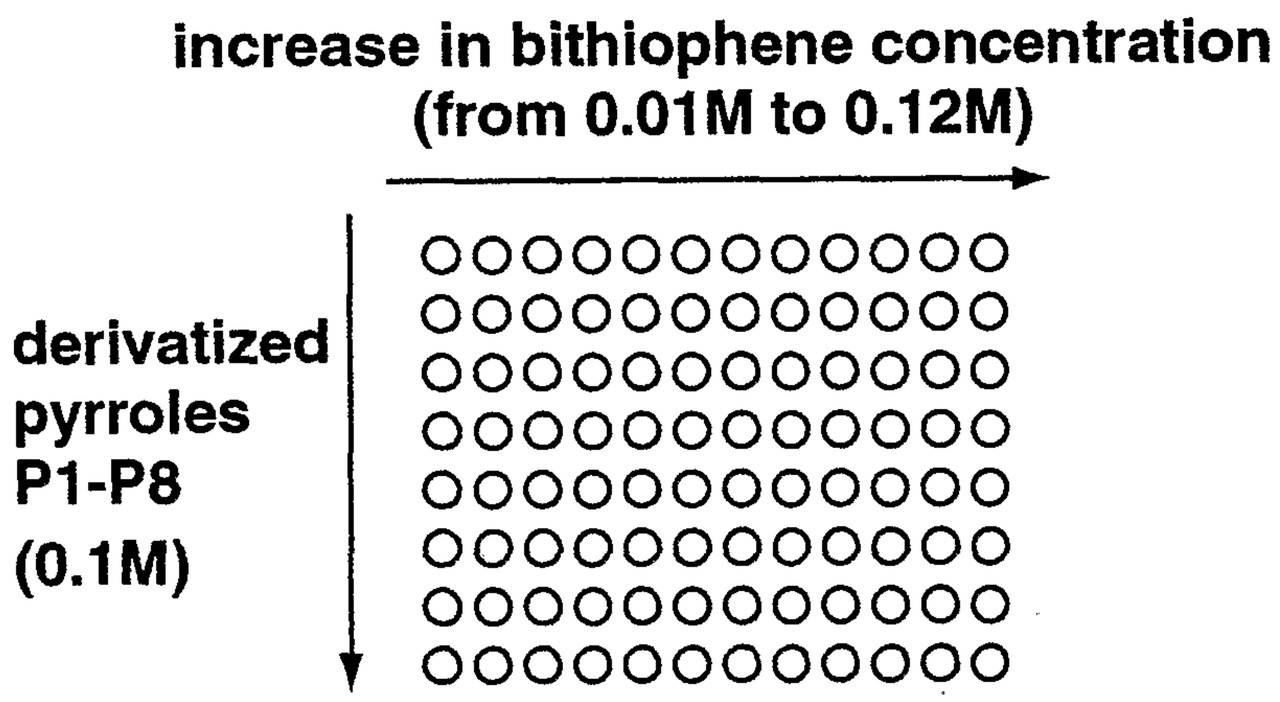

increase in bithiophene concentration
(from 0.01M to 0.12M)
derivatized
pyrroles
P1-P8
(0.1M)

FIG. 13

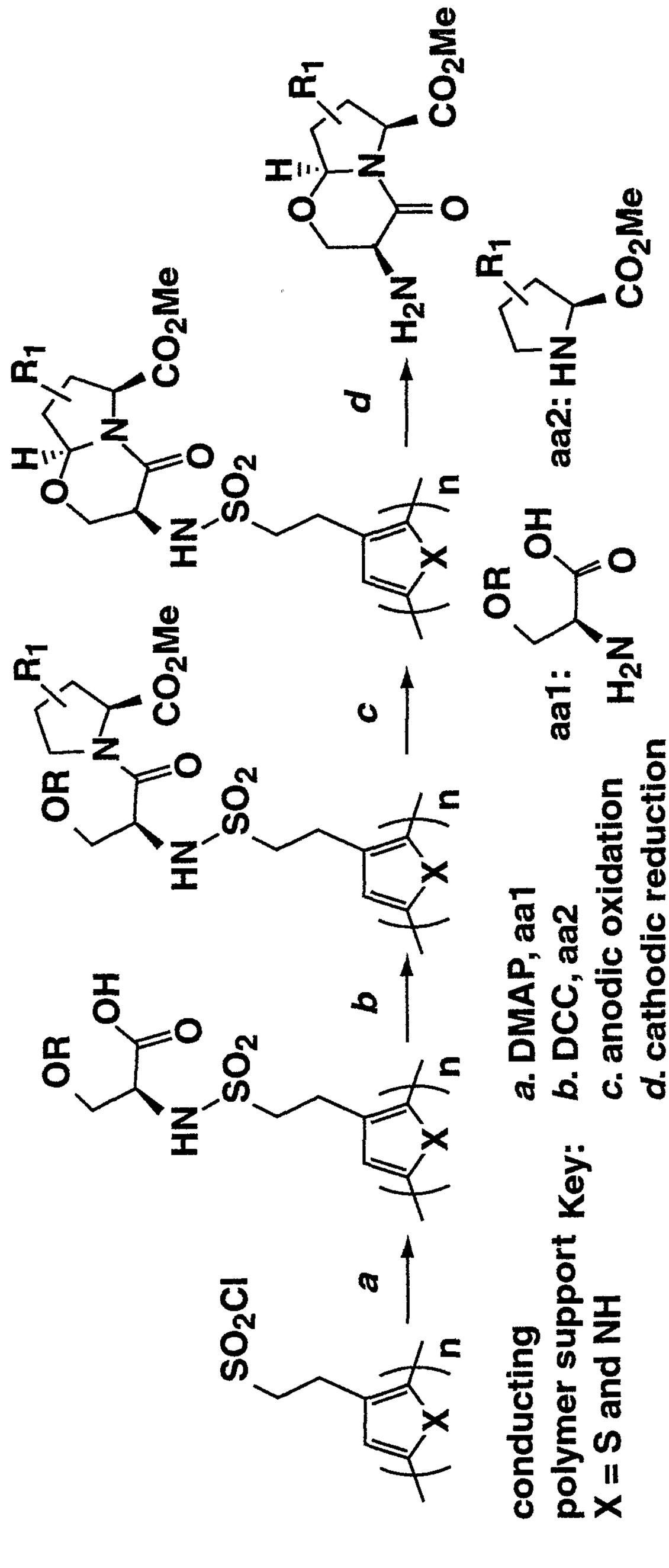

SO2Cl
a
conducting polymer support
X = S and NH
n
X
b
c
d
HN
SO2
OR
OH
O
H2N
CO2Me
R1
aa1:
aa2: HN
Key:
a. DMAP, aa1
b. DCC, aa2
c. anodic oxidation
d. cathodic reduction

FIG. 14

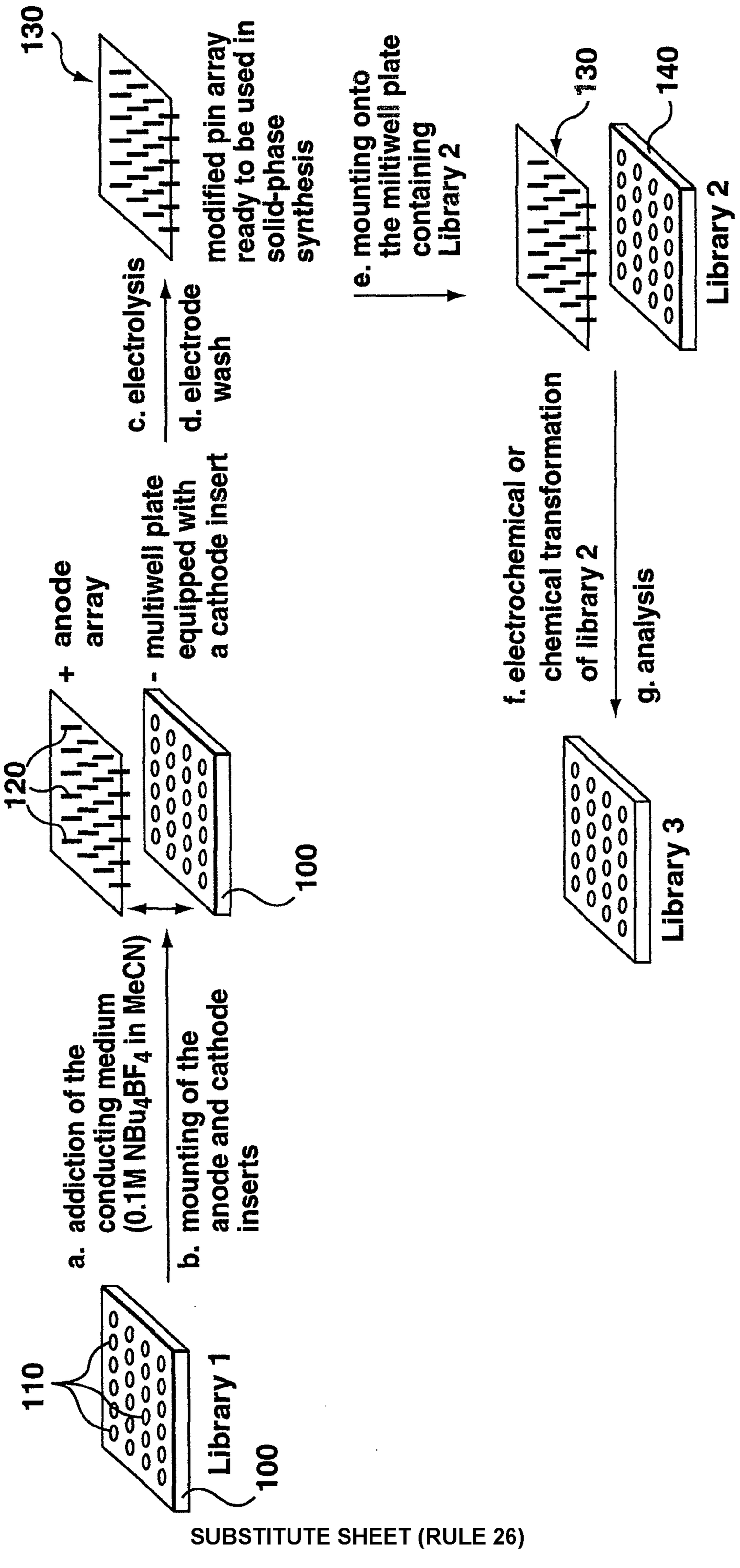
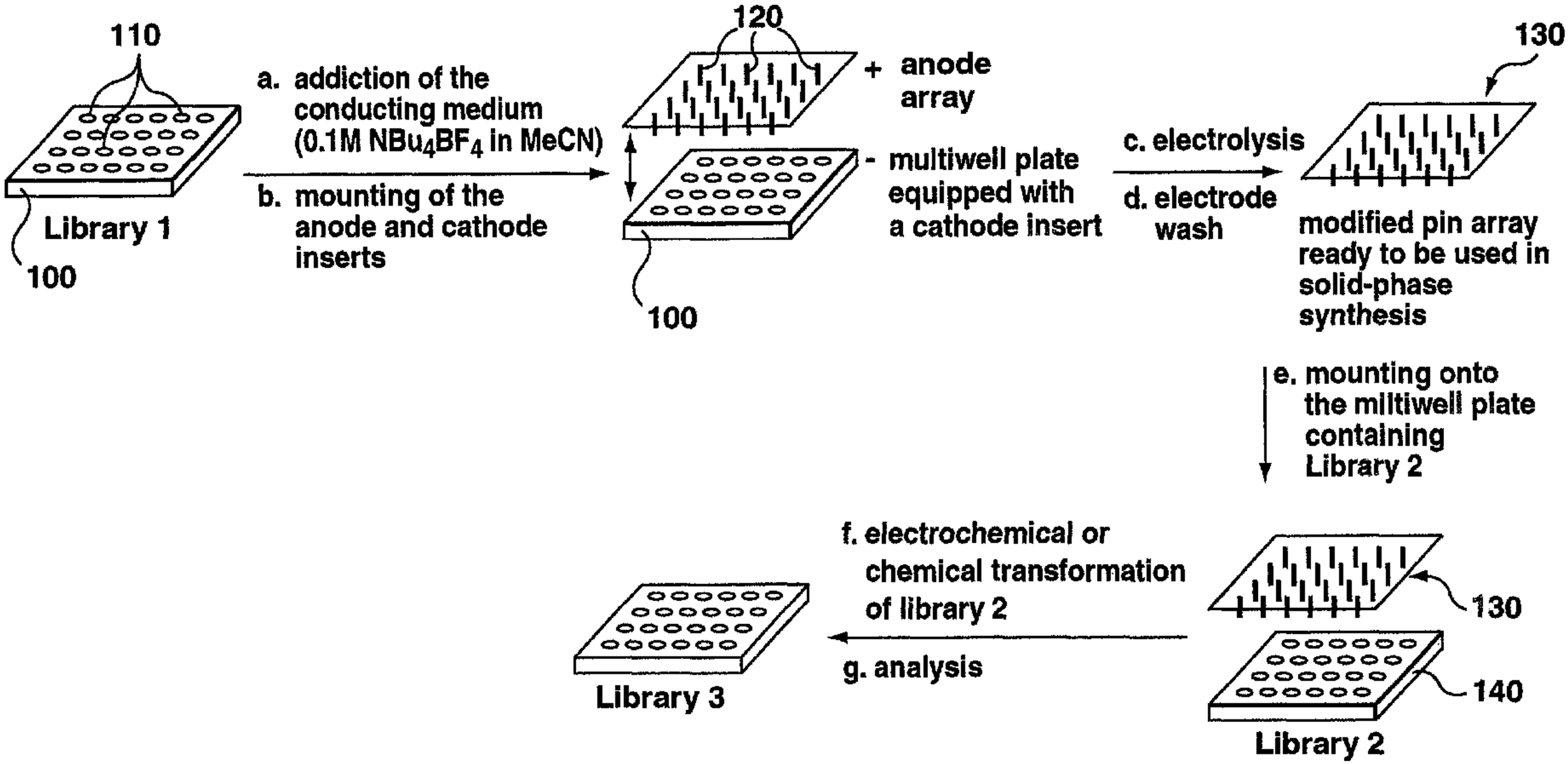

130
modified pin array ready to be used in solid-phase synthesis
e. mounting onto the miltiwell plate containing Library 2
130
140
Library 2
c. electrolysis
d. electrode wash
+ anode array
- multiwell plate equipped with a cathode insert
f. electrochemical or chemical transformation of library 2
g. analysis
120
100
Library 3
a. addiction of the conducting medium (0.1M NBu_4BF_4 in MeCN)
b. mounting of the anode and cathode inserts
110
Library 1
100

FIG. 15


110
Library 1
100
a. addiction of the conducting medium (0.1M NBu_4BF_4 in MeCN)
b. mounting of the anode and cathode inserts
120
+ anode array
- multiwell plate equipped with a cathode insert
100
c. electrolysis
d. electrode wash
130
modified pin array ready to be used in solid-phase synthesis
e. mounting onto the miltiwell plate containing Library 2
f. electrochemical or chemical transformation of library 2
g. analysis
Library 3
130
140
Library 2