

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 September 2010 (23.09.2010)

(10) International Publication Number
WO 2010/107690 A1

(51) International Patent Classification:
C02F 1/28 (2006.01) *C02F 9/00* (2006.01)

(21) International Application Number:
PCT/US2010/027298

(22) International Filing Date:
15 March 2010 (15.03.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/160,467 16 March 2009 (16.03.2009) US

(71) Applicant (for all designated States except US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HAR, Denis** [US/US]; Novartis, One Health Plaza, East Hanover, NJ 07936 (US). **LOO, Mauricio** [US/US]; Novartis, One Health Plaza, East Hanover, NJ 07936 (US).

(74) Agent: **SHIM Sandra**; Novartis, Patent Department, One Health Plaza, Bldg.101, East Hanover NJ 07936 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,

CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))

(54) Title: SEPARATION APPARATUS

(57) Abstract: A separation apparatus (2) for removing heavy metal impurities from a liquid reaction product. The separation apparatus (2) containing a mixture (8) of at least two removal components therein. Each removal component is capable of retaining one or more catalyst impurities and each removal component being substantially retained within the separation apparatus.



WO 2010/107690 A1

Separation Apparatus

The present invention relates to a separation apparatus for removing heavy metal impurities from a liquid reaction product, in particular to a separation apparatus for removing catalyst metal impurities from the product of an organic synthesis.

In organic chemistry of science in general, heavy metals such as Pd, Fe, Rh, Ti, Ag etc are routinely used during a synthesis. Their removal (clean-up) from the process stream produced following the reaction can be a challenging task. There are a variety of methods available to a chemist for such clean-up and these include distillation, extraction and adsorption, however a chemist typically has to use a process of trial and error to develop appropriate conditions and achieve the appropriate product purity in which the heavy metals are present, but at a level below a predetermined limit, for example 5parts per million (ppm).

A typical example of a clean-up process following a reaction catalysed by Pd might be that initially a chemist will try, in a batch-wise manner, using activated carbon, a common Pd scavenger. The activated carbon is added into the reaction mixture which is then heated for a few hours, cooled and filtered. A sample of the filtrate is submitted for Pd content analysis. The result may be better than before, but still unacceptably high so the chemist will have no choice but to perform further clean-up operations until the purity specifications are met. The chemist may have to decide whether to try again with activated carbon, or try a different process or removal component. For example, the

chemist could combine an organic process stream with an aqueous solution of L-cysteine. The mixture could then be heated for a few hours, cooled and the resulting layers separated. The Pd impurity should have migrated
5 into the aqueous layer, assisted by the L-cysteine.

This process can be time consuming and, particularly on a laboratory scale, inconvenient if several different products need to be created for testing, each of which
10 may require a different purification process.

The present invention seeks to provide a more convenient separation apparatus and method.

15 The present invention provides a separation apparatus for removing heavy metal impurities from a liquid reaction product the separation apparatus containing a mixture of at least two removal components therein, each removal component being capable of retaining one or more catalyst
20 impurities and each removal component being substantially retained within the separation apparatus.

By providing a single apparatus which contains a mixture of removal components the number of potential
25 interactions with the heavy metal impurities is increased and the probability of successful purifying is increased. For instance, Pd can take on many forms as it can have an oxidation state of 0, +2 and +4. Also, different organic groups can be attached onto the Pd atoms in the reaction
30 mixture. Different forms of Pd may have a different affinity toward a removal component. For example, some Pd may get removed quickly by bonding rapidly onto the removal component, but others may bond weakly or never at all. By adding at least one further removal component to

create a "cocktail" of removal components more potential modes of interaction are introduced and thus there is a greater chance of successful removal of the Pd, or other heavy metal impurities.

5

Such a mixture of removal components has particular advantages for a lab scale clean up process as costly optimisation of the process, such as selection of an appropriate removal component, is unlikely to be required and there is an increased chance of successful cleanup.

10

The separation apparatus may contain a mixture of at least three removal components therein and may contain at least four removal components. They may be substantially homogeneously mixed within the apparatus, roughly mixed, or substantially separate within the apparatus, for example in substantially separate layers.

15

The separation apparatus may comprise a packed bed in which the removal components are substantially immobilised within a container, such as a separation column. The container being adapted to permit fluid to flow into the container, through the packed bed of immobilised removal components and then out of the container. In such a system the removal components are retained within the separation apparatus. Alternative embodiments may include a fluidised bed arrangement.

20

25

The removal components are each capable of retaining at least one of the heavy metal, possibly catalyst, impurities. At least one of the removal components may be capable of chemically bonding to one or more heavy metal impurities. The removal component may be capable of bonding, substantially permanently or reversibly, to

30

one or more heavy metal impurities. The impurities may be absorbed and / or adsorbed by one or more of the removal components. One or more heavy metal impurities may be filtered from a flow passing through the separation apparatus so that the impurity is physically retained in the removal component and therefore the apparatus.

The removal components may include activated carbon, for example that available from PICA, Quadrapure™ (from Reaxa™), Thiosilica™ (from SiliCycle™), trimercaptotriazine (from Degussa™), and Smopex™ (from Johnson Matthey™). It should be understood that the mixture may include two or more of these, and / or other components. The mixture can be in any proportion, although substantially equal proportions of each removal component may be used in some embodiments.

The heavy metal impurities may include one or more of Pd, Fe, Rh, Ti and Ag. Other heavy metal impurities may also be present. The heavy metal impurities may be present due to their use as a catalyst in an initial reaction process, or for other reasons.

At least one of the removal components may be capable of retaining one or more Palladium impurities and in one embodiment all of the removal components are capable of retaining one or more Palladium impurities. One or more of the removal components may be capable of retaining non-heavy metal impurities in addition to heavy metal impurities.

The invention also provides a process for removing heavy metal impurities from a liquid reaction product, the method comprising the steps of:

- a) passing the reaction product through a separation apparatus to produce a processed product, the separation apparatus being substantially as described above.

The processed product, which may be a mixture, may be passed through the separation apparatus at least one further time. This increases the contact time between the impurity containing liquid and the removal components without the need for the separation apparatus to increase in size. The increased contact time and recycle through the apparatus increases the chances of the impurities being retained within the apparatus. In one embodiment the processed product is passed through the separation apparatus between 9 and 19 additional times.

A separation kit which includes the separation apparatus may further comprise a first reservoir which is initially charged with a reaction product and a pump for moving the reaction product to the separation apparatus. The reaction product may flow down through the separation apparatus under gravity, or may be pumped through the separation apparatus regardless of orientation using the same or an additional pump. In one embodiment the liquid is forced upwards through the separation apparatus against gravity. The liquid leaving the separation apparatus may be taken to a second reservoir, or may be returned to the first reservoir from where it is recycled through the separation apparatus.

It should be noted that the number of times that the liquid is recycled through the separation apparatus is

not an absolute number due to mixing within the reservoir, but is based on the initial volume of liquid which is charged to the system and the volume of liquid which is passed through the separation apparatus during
5 the separation process and assuming a perfectly stirred reservoir. A stirrer may be included in the first reservoir.

The liquid from the first reservoir may be cycled through
10 the apparatus as described above for a predetermined time period rather than a predetermined number of times. Suitable time periods are at least 12 hrs, 24 hrs, 36 hrs and at least 48 hrs.

15 The separation apparatus may comprise a jacketed column in which the mixture of removal components is housed. A temperature controller may be provided to maintain the temperature of the jacket at predetermined elevated level. The predetermined elevated level may be above
20 30°C, may be above 40°C and may be above 45°C. The predetermined elevated level may be below 80°C, may be below 70°C and may be below 60°C. The temperature range may be between 40°C and 60°C. In an alternative embodiment the liquid stream is heated as above before
25 passing through the separation apparatus.

It should be understood that throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or
30 variations such as "comprises" or "comprising", implies the inclusion of the stated integer or step, or group of integers or steps.

The invention will now be further described, by way of example only, with reference to the following drawings in which:

5 Figure 1 shows a schematic view of a separation kit including a separation apparatus.

Figure 1 shows a schematic view of a separation kit 1 including a separation apparatus 2. In this case the
10 separation apparatus 2 is a packed bed column containing a mixture comprising a plurality of removal components.

In use, the liquid product of a reaction to be "cleaned-up" is put into a first reservoir 4. As an example, the
15 reaction may be an organic synthesis reaction in which one or more heavy metal catalysts are used and which subsequently need to be separated from a desired product. From the first reservoir 4 a pump 6 moves the liquid to an inlet 12 of the separation apparatus 2.

20 From the inlet 12, the liquid passes through a distributor 14 and into the packed bed comprising a mixture of removal components 8. The liquid passes upwards through the packed bed and a collector 16
25 collects the liquid that exits the packed bed and channels it to an outlet 10.

From the outlet 16 the processed product is returned to the first reservoir 4 where a stirrer 18 mixes the
30 reservoir contents. The pump 6 continues to pass the liquid through the separation apparatus until a total volume substantially equivalent to between 10 and 20 times the initial volume of content of the reservoir has passed through the separation apparatus 2.

The separation apparatus 2 in this case is a jacketed column and the temperature within the jacket is maintained at about 50 degrees Celsius by a temperature controller 20.

The mixture of removal components 8 in this case comprise a mixture of at least two removal components selected from the following list: activated carbon available from PICA, Quadrapure™ (from Reaxa), Thiosilica™ (from SiliCycle), trimercaptotriazine (from Degussa), and Smopex (from Johnson Matthey).

Specific Examples

15 Experimental Procedure:

The separation apparatus set-up was substantially as shown in Figure 1. Generally, the inlet/outlet of an jacketed glass housing was connected in series to a pump and a reservoir via 1/8inch (3.2mm) PTFE tubing. The temperature of the jacketed housing was maintained using a circulating bath.

Substantially equal quantities of three different removal components were added into a jacketed glass housing. The jacketed glass housing was substantially 25cm in height and had an internal diameter of 1cm.

The removal components added to the housing created a bed volume of about 18mL. The removal components were

- 30 • 3g of activated carbon (PICA-HP100™ from PICAPure™)
- 3g of Thiosilica™ (Thiosilica™ (40-63 μm) from Silicycle™)
- and

- 3g of QuadraPure-TU™ (QuadraPure-TU™ (400-600 μm) from SAFC™)

Example 1

A solution of 10g of reaction mixture containing 4,138
5 ppm of palladium and 100mL of tetrahydrofuran was
prepared and magnetically stirred in the reservoir. The
temperature of the jacketed housing was maintained at
50°C to 55°C using a circulating bath. The pump was
turned on and began circulating the solution through the
10 loop, into the housing and out back to the reservoir at a
flow rate of about 1mL/min. A sample of the solution
(~2mL) was aliquoted from the reservoir at 24h and at 42h
and the Pd count was tested.

15 Results

	Pd count
Sample at 0h	>4,138 ppm
Sample at 24h	5 ppm
Sample at 42h	5 ppm

The procedure was complete. The apparatus was drained of
its THF solution into the reservoir. The Pd free
solution was then concentrated to give the desired
20 product.

Example 2

The same apparatus set up was used as for Example 1 and a
solution was prepared in the same way, but in this case
25 the 10-g reaction mixture initially contained 487 ppm of
Pd. A sample of the solution (~2mL) was aliquoted from
the reservoir at 18h and at 43h and the Pd count was
tested.

Results

	Pd count
Sample at 0 h	487 ppm
Sample at 18h (27°C to 55°C)	74 ppm
Sample at 43h (55°C)	1 ppm

It should be understood that the invention has been
5 described above by way of example only and that
modifications in detail can be made without departing
from the scope of the claims.

Claims

1. A separation apparatus for removing heavy metal impurities from a liquid reaction product the separation apparatus containing a mixture of at least two removal components therein, each removal component being capable of retaining one or more heavy metal impurities and each removal component being substantially retained within the separation apparatus.

10

2. A separation apparatus as claimed in claim 1, in which the separation apparatus contains a mixture of at least three removal components therein.

15

3. A separation apparatus as claimed in claim 2, in which the separation apparatus contains a mixture of at least four removal components therein.

20

4. A separation apparatus as claimed in claim 1, in which the separation apparatus comprises packed bed.

5. A separation apparatus as claimed in claim 1, in which at least one of the removal components is capable of bonding to one or more heavy metal impurities.

25

6. A separation apparatus as claimed in claim 5, in which the removal component is one of activated carbon, Quadrapure™, Thiosilica™, trimercaptotriazine or Smopex™.

30

7. A separation apparatus as claimed in claim 1, in which the removal components are each capable of retaining one or more Palladium impurities.

8. A separation apparatus as claimed in claim 7, in which the separation apparatus contains at least activated carbon, Thiosilica™ and QuadraPure-TU™.

5 9. A process for removing heavy metal impurities from a liquid reaction product, the method comprising the steps of:

a) passing the reaction product through a separation apparatus to produce a processed product, the separation
10 apparatus being as claimed in claim 1.

10. A process as claimed in claim 9, in which the processed product is passed through the separation apparatus at least one further time.

1/1

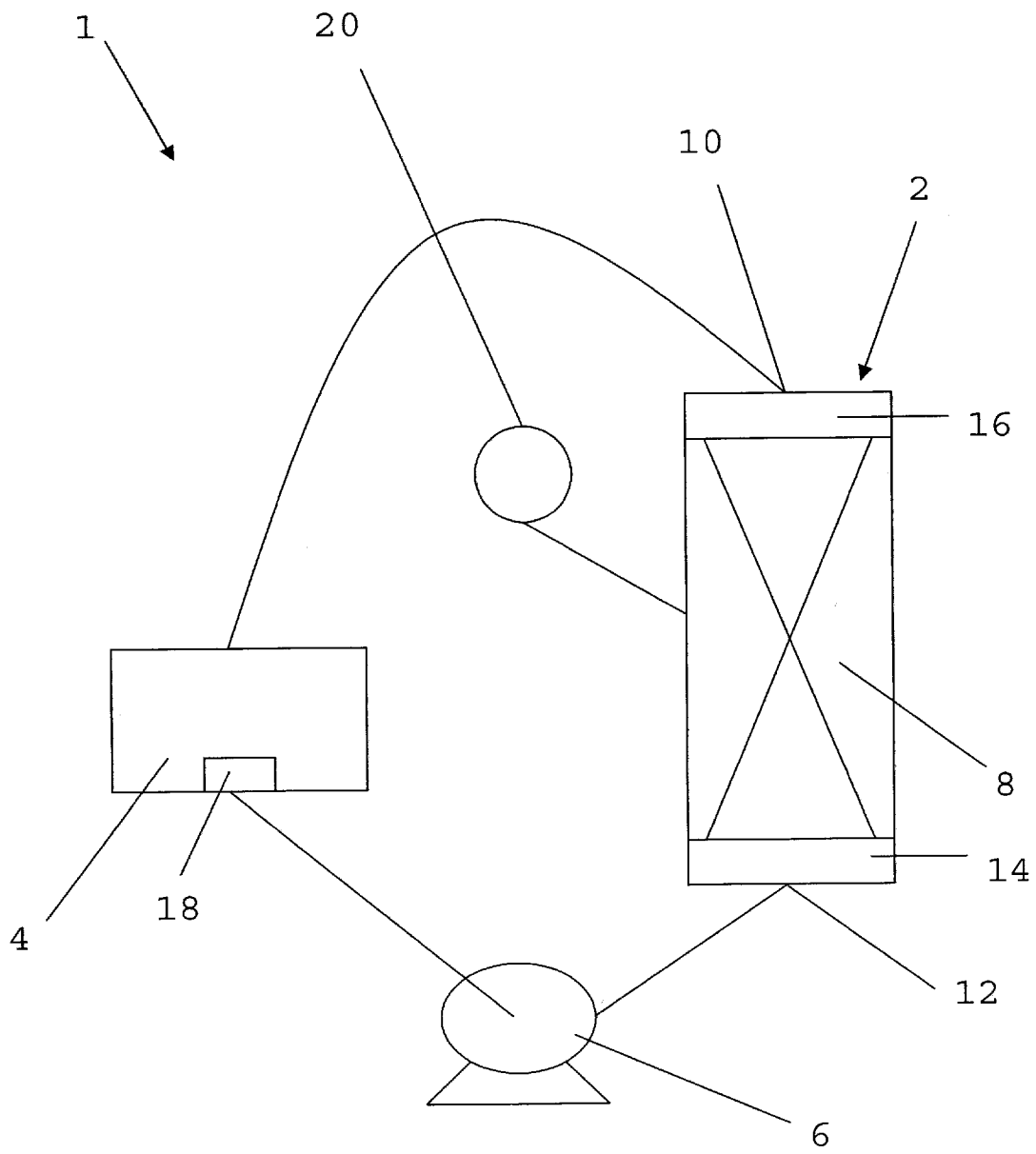


Fig 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/027298

A. CLASSIFICATION OF SUBJECT MATTER
INV. C02F1/28 C02F9/00
ADD.

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)
C02F

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 practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006 0106 248 A1 (M.D. SCALA ET AL.) 18 May 2006 (2006-05-18) paragraph [0013] - paragraph [0020]; claims 1-61	1-10
X	US 5 681 447 A (K.R. MAYCOCK ET AL.) 28 October 1997 (1997-10-28) column 3, line 9 - column 4, line 33; claims 1-15	1-10
X	US 5 275 737 A (D.E. HESKETT) 4 January 1994 (1994-01-04) the whole document	1

☐ 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 but 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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

11 May 2010

Date of mailing of the international search report

21/05/2010

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Luethe, Herbert

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/027298

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 20060106248 A1		NONE	
US 5681447 A	28-10-1997	NONE	
US 5275737 A	04-01-1994	US 5314623 A	24-05-1994