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**Datasheet for the decision  
of 17 April 2018**

**Case Number:** T 1130/13 - 3.3.01

**Application Number:** 08707494.4

**Publication Number:** 2109616

**IPC:** C07F1/02, C07C33/46, C07C2/00

**Language of the proceedings:** EN

**Title of invention:**  
METHOD FOR LITHIUM EXCHANGE REACTIONS

**Patent Proprietor:**  
Lonza AG

**Opponent:**  
Merck Patent GmbH

**Headword:**  
Lithium exchange reactions in microreactor/LONZA

**Relevant legal provisions:**  
EPC Art. 100(a), 56

**Keyword:**  
Inventive step - (yes)  
Fresh ground for opposition - not admitted

**Decisions cited:**

G 0009/91



**Beschwerdekammern**  
**Boards of Appeal**  
**Chambres de recours**

Boards of Appeal of the  
European Patent Office  
Richard-Reitzner-Allee 8  
85540 Haar  
GERMANY  
Tel. +49 (0)89 2399-0  
Fax +49 (0)89 2399-4465

Case Number: T 1130/13 - 3.3.01

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.01**  
**of 17 April 2018**

**Appellant:** Merck Patent GmbH  
(Opponent) Frankfurter Strasse 250  
64293 Darmstadt (DE)

**Respondent:** Lonza AG  
(Patent Proprietor) Münchensteinerstrasse 38  
4052 Basel (CH)

**Representative:** Winter, Brandl, Fürniss, Hübner,  
Röss, Kaiser, Polte - Partnerschaft mbB  
Patent- und Rechtsanwaltskanzlei  
Alois-Steinecker-Strasse 22  
85354 Freising (DE)

**Decision under appeal:** **Decision of the Opposition Division of the  
European Patent Office posted on 13 March 2013  
rejecting the opposition filed against European  
patent No. 2109616 pursuant to Article 101(2)  
EPC.**

**Composition of the Board:**

**Chairman** A. Lindner  
**Members:** M. Pregetter  
L. Bühler

## Summary of Facts and Submissions

- I. European patent No. 2 109 616 is based on European patent application No. 08707494.4, filed as an international application published as WO2008/095646.
- II. Independent claim 1 of the patent in suit as granted reads as follows:

"1. A method for carrying out a lithium exchange reaction comprising mixing at least two fluids, one of the at least two fluids comprising a compound able to react with an lithium exchange reagent in a lithium exchange reaction (1<sup>st</sup> reactant), and another fluid comprising a lithium exchange reagent (2<sup>nd</sup> reactant), said mixing taking place in a microreactor (6) comprising at least one flow path (1) for one of the at least two fluids (A) comprising either the 1<sup>st</sup> or 2<sup>nd</sup> reactant, said flow path(s) comprising at least two reaction regions (2), each reaction region comprising an injection point (3) for feeding the other one of the two fluids (B) comprising either the 2<sup>nd</sup> or 1<sup>st</sup> reactant, a mixing zone (4) in which the at least two fluids contact each other and a reaction zone (5), and wherein the microreactor optionally provides one or more additional residence time volumes or has additional residence time volumes attached, and wherein in said method one of the at least two fluids comprising either the 1<sup>st</sup> or 2<sup>nd</sup> reactant establishes a first flow and wherein at other one of the at least two fluids comprising either the 2<sup>nd</sup> or 1<sup>st</sup> reactant is injected into said first flow at least at two injection points (3) along said flow path(s) (1) in a way such that at each injection point only a fraction of the amount necessary to reach completion of the lithium

exchange reaction is injected."

III. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(1) EP-A-1010703

(3) J Hagen: "Chemiereaktoren, Auslegung und Simulation", 2004, Wiley-VCH, pages 134-152

(4) M Baerns, H Hofmann, A Renken: "Chemische Reaktionstechnik, Lehrbuch der Technischen Chemie Band 1", 2. Auflage, 1992, Thieme, pages 400-419

(6) DE-A-39 26 466

(8) W Ehrfeld, V Hessel, H Löwe: "Microreactors New Technology for Modern Chemistry", 2000, Wiley-VCH, page 1

(9) Edward Furimsky, Catalysts for Upgrading Heavy Petroleum Feeds, Studies in surface science and catalysis, volume 169, 2007, page 45

(10) experimental report, pages 6-11 of the letter dated 16 March 2018

IV. In opposition proceedings the opponent sought revocation of the patent in suit for lack of inventive step pursuant to Articles 56 and 100(a) EPC. The opposition division rejected the opposition.

V. The opponent (appellant) lodged an appeal against this decision. In its statement of grounds of appeal, the appellant disputed the analysis and conclusions of the

opposition division with respect to inventive step.

- VI. Oral proceedings were held before the board on 17 April 2018.
- VII. The appellant's arguments, in so far as they are relevant to the present decision, may be summarised as follows:

*Admission of late filed documents*

Neither the filing of document (8) nor the filing of experimental data (10) introduced new facts into the proceedings. Document (8) and the experimental data (10) supported only arguments that had already been raised in opposition and appeal proceedings.

The definition of what constituted a microreactor was important for the outcome of the appeal proceedings, such a definition could be found in document (8). The issue had gained importance due to the arguments presented by the respondent in appeal. Document (9) could not shed any light on the definition of a microreactor since it related to a very special technical field. Document (9) should not be admitted into the proceedings.

It had not been possible to submit the experimental data (10) at an earlier point in time, since the reactor technology and configuration had first to be established at the appellant's company.

*Sufficiency of disclosure*

The dimensions of the microreactor were not clearly defined. The experimental data (10) showed that the

claimed effects could not be obtained with the set-up chosen. The combination of these two facts led to an undue burden for the skilled person when trying to re-work the claimed method. Sufficiency of disclosure was thus not given.

*Inventive step*

Document (1) represented the closest prior art.

The only difference between the teaching of document (1) and the subject-matter of claim 1 of the patent in suit was the injection of one of the reactants at at least two injection points.

The patent in suit aimed at solving two partial problems, the improvement of selectivity and the avoidance of hot spots. The formation of hot spots was however not a problem that actually arose. Neither in the examples according to the invention nor in the comparative example could any indication of the occurrence of hot spots be found. From table 1 of the patent in suit it was clear that at all three temperatures the same conversion and the same yield was achieved. For the remaining problem of selectivity, a small increase in selectivity, albeit linked to a decrease in yield, existed for the very specific example described in the patent in suit.

The example of the patent in suit related to a specific lithium exchange reaction using very special reactants and thus was not representative for lithium exchange reactions in general. This single, very specific example did not provide sufficient evidence that the selectivity of lithium exchange reactions in general had been improved.

The objective technical problem could thus be seen as the provision of an alternative way of conducting a lithium exchange reaction.

The solution, i.e. the provision of two injection points, was obvious. Document (1) already disclosed a tubular reactor having two injection points (figure 2). In the explicit context of microreactors, the possibility of having several injection points was also known from document (6) (column 1, line 66, to column 2, line 6). The constructional means for carrying out a reaction relying on at least two injection points were thus disclosed in the (closest) prior art. Furthermore, the common general knowledge, represented by the two textbooks (3) and (4), taught the skilled person, a chemical engineer, to conduct certain reactions in a cross-flow mode. Document (4), on page 400, second paragraph, stated that the choice of reactor type was crucial for achieving high selectivity and high yields. On page 404, an example concerning parallel reactions carried out in a cross-flow reactor was discussed in detail. In figure 10.33, selectivity and yield were discussed in view of cross-flow reactors having various numbers of injection points. An example with five injection points was disclosed. Document (3), in the context of complex reactions, provided on page 146 indications for the selection of the most suitable reactor type (table 6-3). Table 6-3 recommended the use of a cross-flow reactor for a reaction followed by a subsequent reaction ("Folgereaktion"), especially in view of selectivity and yield. Thus, the common general knowledge of the skilled person, represented by the teaching of documents (3) and (4), inevitably led to the use of a cross-flow reactor for the reaction types under consideration. The subject-matter of claim 1 of



the patent in suit did not involve an inventive step.

VIII. The respondent's (patent proprietor's) arguments, in so far as they are relevant to the present decision, may be summarised as follows:

*Admission of late-filed documents*

Document (8) and the experimental data (10) filed with letter dated 16 March 2018 should not be admitted, since they were late-filed. As shown by document (9) there was no general consent in the art on the dimensions of a microreactor. The filing of experimental data one month before the date of oral proceedings rendered it impossible to react adequately, e.g. by redoing the experiments or by carrying out appropriate other experiments. If the experimental data (10) were admitted, an adjournment of the oral proceedings would be necessary.

*Sufficiency of disclosure - new ground for opposition*

The respondent did not agree to the introduction of the ground for opposition according to Article 100(b) EPC.

*Inventive step*

Starting from document (1) as the closest prior art, there were at least two differences. Document (1) did not teach the use of a microreactor and did not suggest providing at least two injection points for the same reactant. The effects due to these differences were the prevention of the formation of hot spots and the improvement in selectivity due to less formation of side-products.

The problem to be solved was thus the provision of an improved method for lithium exchange reactions that could be better controlled.

First of all, it was important to keep in mind that claim 1 of the patent in suit defined a method for carrying out a lithium exchange reaction. Document (1) related to the synthesis of aryl metal compounds by deprotonation of aromatic compounds using a suitable base or by halogen-metal exchange. Lithium exchange reactions were thus only one alternative listed in document (1). Furthermore, since document (1) did not concern microreactors and actually related to kinetically slower reactions, hot spots were not problematic. Hot spots were a particular problem of microreactors.

Document (6) aimed at improving yield and consequently would not be consulted by a skilled person trying to improve selectivity.

Document (3), in table 6-3, suggested the use of a cross-flow reactor for reactions involving a subsequent reaction. In the present case the subsequent reaction was the formation of a side-product, i.e the teaching of document (3) led to the opposite results of those sought.

Document (4) did not relate to microreactors. Also, its teachings were general and the information provided on page 404 did not apply to lithium exchange reactions, which were very fast reactions.

Consequently, there was no teaching in the prior art that would lead a skilled person to carry out a lithium exchange reaction in a microreactor having at least two

injection points. The subject-matter of claim 1 of the patent in suit involved an inventive step.

IX. The final requests of the parties were as follows:

The appellant (opponent) requested that the decision under appeal be set aside and that the European patent No. 2109616 be revoked.

The respondent (patent proprietor) requested that the appeal be dismissed (main request) or, alternatively, that the patent be maintained on the basis of the claims of one of auxiliary requests I and II filed with the reply to the statement of grounds of appeal.

### **Reasons for the Decision**

1. The appeal is admissible.
2. *Admission of documents (8) and (9) and of the experimental data (10)*
- 2.1 *Documents (8) and (9)*

Documents (8) and (9) were submitted at a very late stage of the proceedings and after oral proceedings had been arranged. Both documents were filed with the intention to provide definitions for microreactors, especially in view of showing the dimensions of microreactors. However, the two documents disclose different dimensions. The assessment of the conflicting information disclosed in these documents would have given rise to a new debate. The documents could thus not reasonably be dealt with at the oral proceedings.

Consequently, documents (8) and (9) were not admitted in accordance with Article 13(1) and (3) RPBA.

## 2.2 *Experimental data (10)*

The appellant filed, for the first time in the proceedings, experimental data with the letter dated 16 March 2018.

Notice of opposition was filed on 24 May 2011, i.e. nearly seven years prior to the submission of the experimental data (10). The decision of the opposition division, issued on 13 March 2013, rejected the opposition. On the same day, 13 March 2013, an appeal was filed by the opponent, followed by the statement setting out the grounds of appeal dated 17 May 2013, i.e. nearly five years prior to the submission of the experimental data (10). The reply to the statement of grounds of appeal, which was the only submission by the respondent relating to substantial issues in appeal proceedings, was submitted on 6 February 2014, i.e. more than four years prior to the filing of the experimental data (10). At no point in time during these seven years was the intention to file experimental data announced, nor was any indication given that the establishment of the microreactor technology with a reactor having at least two injection points was time-consuming.

The board notes that the statement of grounds of appeal and the reply shall contain a party's complete case (Article 12(2) RPBA). If an argument requires further support, e.g. by experimental data, it is the appellant's obligation to file such data as soon as possible. The filing of experimental data clearly extends the appellant's case. Any amendment to a

party's case after it has filed its grounds of appeal or reply may be admitted and considered at the board's discretion. The discretion is to be exercised in view of *inter alia* the complexity of the new subject-matter submitted, the current state of the proceedings and the need for procedural economy (see Article 13(1) RPBA).

In the present case, the filing of the experimental data (10) at this late stage of the proceedings was not occasioned by new issues or aspects raised either in the contested decision, or by the respondent or the board in the appeal proceedings. The very late point in time at which said data was filed therefore contravenes the appellant's obligation to conduct proceedings before the EPO in good faith (G 2/97, OJ 1999, 123, point 4.2) which requires *inter alia* that the parties complete their relevant submissions at the earliest possible moment in the proceedings. In the present case, the appellant was in a position to make its submission earlier and could have been expected to do so under the circumstances.

Additionally, the board notes that the experimental data (10) were submitted only four weeks before the oral proceedings before the board. Four weeks is too short a time to give the respondent the opportunity to check the data for validity and to react properly. A proper reaction to the data would entail at least its repetition and, depending on the result, even the preparation of counter-experiments. If the experimental data (10) had been admitted into the proceedings, an adjournment of the oral proceedings would have had to be considered. According to Article 13(3) RPBA, amendments sought after oral proceedings have been arranged shall not be admitted if they raise issues that may necessitate an adjournment.

Consequently, in exercise of its discretion under Article 13 RPBA, the board has decided not to admit the experimental data (10) in application of Article 13(1) and (3) RPBA.

3. *New ground for opposition*

The ground for opposition pursuant to Article 100(b) EPC was not invoked in the opposition proceedings. According to decision G 9/91 (OJ EPO 1993, 408) fresh grounds for opposition may not be introduced at the appeal stage unless the patent proprietor agrees to their introduction (G 9/91, point 18). As the patent proprietor did not give its consent, the ground for opposition pursuant to Article 100(b) EPC cannot be introduced.

4. *Inventive step*

- 4.1 The subject-matter of the patent in suit relates to lithium exchange reactions. The aim is to improve and control these chemical reactions, especially increase selectivity (paragraphs [0001] and [0004]). A method is provided whereby one of the reagents is injected into the flow path of the other reactant at several points in such a way that at each injection point only a fraction of the amount necessary to reach completion of the lithium exchange reaction is injected (paragraph [0006], claim 1). By feeding only a fraction of the amount of reactant necessary to reach completion of the lithium exchange reaction while using more than one injection point, an increase in the number of hot spots is created, while in parallel the temperature rise in each hot spot is reduced. In addition, since one of the two reactants is presented in dilution, the formation

of side-products is reduced and yields are increased (paragraph [0009]).

- 4.2 The opposition division and all parties considered that document (1) represented the closest prior art.

Document (1) defines a method for the preparation of aryl metal compounds by halogen-metal exchange of halogenated aromatic compounds using a suitable metalation reactant, and the reaction thereof with electrophiles, characterised in that the aryl metal compounds are prepared in a flow reactor (claim 1). Claim 12 defines lithiation. Figure 1 depicts a scheme of the process. The two reactants for the metalation/lithiation are added through pumps (1) and (2) into a continuous flow reactor, the reactants are mixed in a mixer (9) and condensed in a product condenser (10). Thereafter the metalation product obtained in this way is introduced into a solution or melt of an electrophilic reagent for further reaction (figure 1, paragraphs [0081] and [0082]). The further reagent, the electrophil may be added through pump (12) (figure 2 and paragraph [0083]). The mixer (9) may be a micro-mixer (paragraph [0085]).

- 4.3 Claim 1 of the patent in suit differs at least in that one of the reactants is introduced into the flow reactor at several injection points in several fractions.

- 4.4 Lithium exchange reactions are extremely fast reactions and lead to a rise in temperature in the reaction zone, i.e. to the formation of a hot spot. The actual temperature rise will necessarily depend on the conversion rate in this zone and on the cooling provided. The appellant has referred to table 1 of the

patent in suit which provides information on temperatures. The board notes that table 1 of the patent in suit provides merely information on the temperature of the fluid for the "thermal adjustment of the microreactor" (T-MR). No temperatures of the reaction zones themselves are disclosed. From the temperatures of table 1 of the patent in suit it is not possible to conclude that no hot spots are formed. One can even generally assume that, under comparable other process conditions, the actual temperature rise in the reaction zone will be reduced in the examples according to the invention due to the lower conversion rate linked to the reduced presence of one of the reactants. Concerning the selectivity of the reactions, table 1 of the patent in suit shows an increase in selectivity for the examples according to the invention. Whether or not this increase in selectivity is directly due to the avoidance of high temperature rises in the hot spots cannot be established. However the fact remains that the data shows an improved effect, i.e. an improved selectivity.

The appellant has questioned whether the set-up of the examples of the patent in suit is suitable to show an effect over the whole scope of claim 1 as granted.

One line of argument presented in this context concerns considerations as to whether the selection of the reactant for the continuous flow path and the directly associated selection of the reactant to be introduced at the injection points has an influence on the effect of improved selectivity. As this line of argument is not further supported, e.g. by mechanistical or other theoretical considerations, it has to be taken as a mere allegation.



The second point brought forward by the appellant concerns the reactants of the example of the patent in suit. The appellant argued that p-fluorobenzaldehyde was a very special reactant since it allowed for a further lithiation, i.e. it allowed for the formation of a side-product that could not be formed in every lithiation reaction. The board notes in this context that side-reactions can occur at various points in time and may concern educts, possible intermediate products and the desired end-products. Various combinations of parallel reactions and subsequent reactions can be envisaged. In the absence of evidence that not all lithium exchange reactions may be accompanied by the formation of side-products, this line of argument cannot be adopted.

Consequently, the board bases its conclusion on the following two points:

- It is plausible, due to theoretical considerations, that the temperature rise in the hot spots formed after the injection of the second reactant is less severe. The reaction conditions are thus more controlled.
- It has been shown at least for one example that the selectivity is higher when the second reactant is injected as a fraction of the amount necessary to reach completion of the lithium exchange reaction at several, here three, injection points.

The board concludes that the appellant has not provided any well-founded arguments showing that the effect is not present over the whole scope of the claim.

- 4.5 The problem to be solved is thus the provision of a more controlled method for carrying out lithium exchange reactions leading to a higher selectivity.

The solution to this problem lies in the provision of a method that relies on injecting the second reactant of the lithium exchange reaction in fractions at at least two injection points. As discussed above (see point 4.4) the problem is considered to be solved.

4.6 Several documents have been invoked to show that it was obvious to carry out a lithium exchange reaction, and especially a lithium exchange reaction having improved selectivity, in a continuous flow reactor having more than one point of injection.

The appellant has argued that the claimed method was obvious in view of document (1) itself, since document (1) already depicted a reactor having two points of injection. The board cannot follow this argument. The second point of injection (12) is clearly intended for the second step of the method claimed in document (1), i.e. the addition of the electrophile (see paragraph [0083]). There is no indication in document (1) that said second point of injection could be used to add a fraction of one of the reactants of the metalation reaction.

Document (3) relates to kinetic parameters of various reaction types. In table 6-3, recommendations for the selection of the reactor type are given for simple and complex reaction types. The appellant has pointed to the second-last reaction, a reaction type involving a subsequent reaction ("Folgereaktion"). Said reaction type has been said to be the pertinent one for lithium exchange reactions and thus the reaction type the skilled person would consider. For this type of reactions table 6-3 recommends the use of a cross-flow reactor, especially for optimising selectivity. The board cannot follow this line of argument. The reaction type referring to a first reaction and a subsequent

reaction is not the reaction type that corresponds to a lithium exchange reaction as such. In case of lithium exchange reactions the subsequent reaction would be a side-reaction leading to less of the desired product and to more side-product(s) and thus to a decrease in selectivity. Consequently, the disclosure in document (3) would not be considered to be pertinent for lithium exchange reactions by the skilled person.

Document (4) discusses the selection of reactor types for complex reactions (chapter 2). In example 10.8, on page 404, parallel reactions are discussed. The first reaction takes place between  $A_1$  and  $A_2$ , the second reaction between  $A_1$  and  $A_1$ . Figure 10.33 provides information on the obtainable yields and selectivities for such parallel reactions in view of several cross-flow reactor types. The appellant has pointed to the favourable selectivity values for a cross-flow reactor having five injection points. The board notes however that a parallel reaction as disclosed in document (4) would lead to undesired side-products in a lithium exchange reaction, and thus, in the case of a lithium exchange reaction, to a decrease in selectivity. A person skilled in the art would thus disregard the disclosure of document (4).

Neither parallel reactions (as in the cited passages of document (4)) nor subsequent reactions (as in the cited passages of document (3)) are sought in the present case. On the contrary, the parallel and the subsequent reactions are exactly the type of reactions that are the cause of the formation of side-products and thus lead to an decrease in the selectivity of the lithium exchange reaction. Consequently, the cited passages of documents (3) and (4) would not have provided any incentive for the skilled person to employ a cross-flow

reactor for carrying out lithium exchange reactions.

Document (6) was mentioned by the appellant with mere reference to one passage, column 1, line 66, to column 2, line 6, which shows that several points of addition and mixing of a second reactant were known for micro-reactors. The appellant has not provided any argumentation why the skilled person would use this embodiment of document (6) when trying to improve the selectivity of a lithium exchange reaction.

In sum, none of the documents cited by the appellant leads a skilled person to the use of a reactor having more than one injection point for the second reactant of a lithium exchange reaction.

4.7 The appellant further argued that the enhanced selectivity shown in Table 1 of the patent in suit was accompanied by a reduced conversion so that the overall yield did not significantly change. This appears to be correct but does not change the conclusions about inventive step reached in paragraphs 4.1 to 4.6 above. In this context, it is emphasised that the problem to be solved is not based on increased yields but concerns the provision of a more controlled method for carrying out lithium exchange reactions leading to higher selectivity (see paragraph 4.5 above).

4.8 The subject-matter of claim 1 of the patent in suit involves an inventive step (Article 56 EPC).

## **Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated