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D E C I S I O N
of 5 June 1996

Case Number: T 0412/94 - 3.3.1

Application Number: 90300938.9

Publication Number: 0381434

IPC: C07D 249/08

Language of the proceedings: EN

Title of invention:
Process for producing optically active alcohol

Applicant:
SUMITOMO CHEMICAL COMPANY, LIMITED

Opponent:
-

Headword:
Optically active alcohols/SUMITOMO

Relevant legal provisions:
EPC Art. 56

Keyword:
"Novelty - yes"
"Inventive step - yes - improvement made credible"

Decisions cited:
T 0181/82, T 0197/86

Catchword:
-



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Boards of Appeal

Chambres de recours

Case Number: T 0412/94 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 5 June 1996

Appellant: SUMITOMO CHEMICAL COMPANY, LIMITED
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Decision under appeal: Decision of the Examining Division of the European Patent Office posted 28 December 1993 refusing European patent application No. 90 300 938.9 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: A. J. Nuss
Members: P. P. Bracke
W. Moser

Summary of Facts and Submissions

- I. The appeal lies from the decision of an Examining Division, posted on 28 December 1993, refusing European patent application No. 90 300 938.9, published as EP-A-0 381 434.
- II. The Examining Division held that the sets of claims according to the then pending requests did not meet the requirement of inventive step, since the claimed subject-matter was obvious in the light of the teachings of documents
- (1) EP-A-0 171 175 and
 - (2) EP-A-0 142 566.
- III. More particularly, the Examining Division considered that it was not credibly demonstrated that the conversion rate of the prochiral ketone into the asymmetric alcohol was improved by the claimed process, because comparison was not made with what in view of T 181/82 (OJ EPO, 1984, 401) should be considered as the closest state of the art, namely one of the examples given in document (2).

Consequently, the problem to be solved by the claimed process could only be seen in providing a further process for preparing optically active alcohols from a prochiral ketone. Since the claimed process differed from those described in document (2) only by the solvent used for preparing the reducing agent and since it was known from that document that the solvent used in producing the reducing compound was not particularly critical as long as it did not take part in the reaction, the Examining Division held that it was obvious to try other solvents. More particularly, the

Examining Division found that, since diglyme was cited in document (2) as a suitable solvent, it was obvious to try another ether as a solvent in the process described in document (2).

The Examining Division also observed that even if an unexpected effect in relation to the reduction of one particular prochiral ketone with a particular boron hydride reducing agent were shown, such effect could hardly be expected to be achieved for the whole claimed scope.

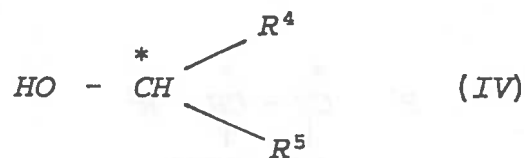
IV. The Appellant (Applicant) submitted that the problem to be solved by the claimed process was to improve the conversion of a prochiral ketone compound into an optically active alcohol in a prescribed reaction time or, alternatively, to shorten the reaction time required for a particular conversion.

In order to credibly demonstrate that this problem was indeed solved, the Appellant filed, together with the statement of the grounds of appeal, an "Experimental Report", describing in particular

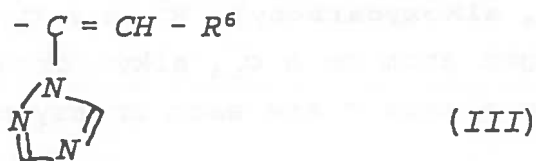
- experiment E repeating the process of example 6 in document (2),
- experiments F and G essentially differing from experiment E by the presence of dimethyl sulfide or diethyl ether,
- experiment J differing from experiment E by the molar ratio of the ketone to the reducing agent used and
- experiment K differing from experiment J by the presence of dimethyl sulfide.

V. In reply to a communication from the Board pursuant to Article 110(2) EPC, the Appellant, with a letter dated 11 September 1995, filed six sets of claims as a main request and as first to fifth auxiliary requests respectively. Subsequently, with letter of 24 May 1996 the Appellant filed a slightly revised set of claims according to the main request and a description adapted to this set of claims. The only independent claim according to the **main request**, consisting of 7 claims, read (emphasis added):

"1. A process for producing an optically active alcohol represented by the general formula (IV)

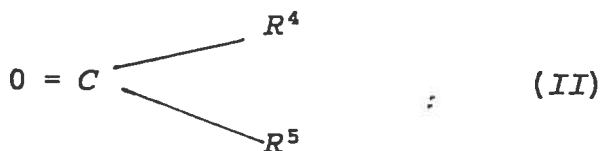


wherein R⁴ and R⁵ are different from one another and each is a C₁₋₆ alkyl group, a C₆₋₁₇ aryl group, a C₇₋₁₁ aralkyl group or a 2-substituted-1-triazoleethylene group represented by the general formula (III)



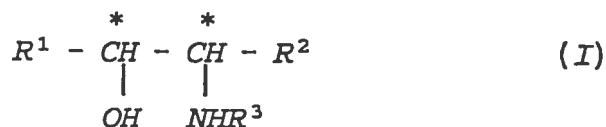
(R⁶ is a halogen- or haloalkyl-substituted or unsubstituted phenyl group or a cycloalkyl group) and the carbon atom having a mark * is an asymmetric carbon atom

by reducing a prochiral ketone compound represented by the general formula (II)



wherein R⁴ and R⁵ are as defined above

with a boron hydride type asymmetric reducing agent modified with an optically active alcohol represented by the general formula (I)



(wherein R¹ is an aryl group selected from a phenyl group optionally substituted with halogen, C₁₋₅ alkyl, C₁₋₅ alkoxy, cyano, C₆₋₁₀ aryloxy, C₇₋₁₀ aralkyloxy or C₁₋₆ alkoxy carbonyl and a naphthyl group optionally substituted with halogen, C₁₋₅ alkyl, cyano, C₁₋₅ alkoxy or C₁₋₅ alkoxy carbonyl, R² is a C₁₋₅ alkyl group, R³ is a hydrogen atom or a C₁₋₅ alkyl group, and the carbon atoms having a mark * are each an asymmetric carbon atom),

which asymmetric reducing agent is obtained by reacting

(A) an optically active amino alcohol represented by the general formula (I) and an acid, or a salt of the optically active amino alcohol represented by the general formula (I) and an acid, with

(B) a metal borohydride,

characterised in that the said reaction of components (A) and (B) is carried out in the presence of

(C) at least one compound selected from sulfides, cyclic ethers and ethers of mono alcohols".

VI. The Appellant requested the cancellation of the contested decision and the grant of a patent on the basis of any of the sets of claims according to the main request or the first to fifth auxiliary requests filed with letter of 24 May 1996.

Reasons for the Decision

1. The appeal is admissible.

2. *Main request*

2.1 Amendments

Present Claim 1 essentially differs from Claim 2 as originally filed by the features contained in the text in bold, which correspond with the following passages in the application as filed (as published):

- Claims 4, 5 and 7,
- page 5, lines 8 to 15 (page 5, lines 2 to 5) and
- page 14, lines 22 to 25 (page 7, lines 22 to 23).

The additional features mentioned in claims 2 to 7 were cited in the following passages in the application as filed (as published):

- present Claim 2: Claims 2, 3 and 4,
- present Claim 3: page 13, lines 11 to 23 (page 7, lines 2 to 8),
- present Claim 4: page 13, lines 24 to 28 (page 7, lines 9 to 10),
- present Claim 5: page 13, line 28, to page 14, line 3 (page 7, lines 11 to 12),
- present Claim 6: page 8, line 12, and page 3, lines 4 to 7 (page 5, line 48, and page 4, lines 20 to 21) and
- present Claim 7: page 7, lines 17 to 21 (page 5, lines 36 to 38).

From this it follows that these amendments comply with the requirements of Article 123(2) EPC.

2.2 Novelty

Neither in document (1) nor in document (2) is a process disclosed as defined in Claim 1, wherein the reducing agent is obtained by reacting (A) with (B) **in the presence of a sulfide, a cyclic ether or an ether of a mono alcohol**. Furthermore, none of the other cited documents discloses the combination of all the features of Claim 1. Consequently the Board is satisfied that the claimed process is novel in respect of the cited state of the art (Article 54 EPC).

2.3 Inventive step

- 2.3.1 The Board considers document (2) to be the closest state of the art. This was also accepted by the Appellant.

Document (2), which corresponds with the state of the art mentioned in the application in suit, is concerned with the finding that optically active boron hydride-type reducing agents obtained by reacting an optically active amino alcohol with an acid and a metal borohydride were useful as asymmetric reducing agents for converting prochiral ketones into optically active alcohols (see the description of the application in suit, page 3, lines 14 to 18, and document (2), page 5, line 24 to page 6, line 9).

- 2.3.2 In view of the method disclosed in document (2), the problem underlying the invention must be seen in the development of a process wherein a prochiral ketone compound is efficiently reduced to an optical active alcohol at a high optical yield (see also page 7, lines 34 to 36, of the application in suit). On the basis of the filed evidence the Board interprets the efficient reduction as improving the conversion in a prescribed reaction time or, alternatively, as shortening the reaction time required for a particular conversion (see point 2.3.3 below). This is in complete conformity with the Appellant's interpretation given during the appeal procedure.

According to Claim 1, this problem is solved by synthesising the asymmetric reducing agent from an optically active amino alcohol and a metal borohydride **in the presence of a component (C)**, namely a sulfide, a cyclic ether or an ether of a mono alcohol.

- 2.3.3 When assessing inventive step, the first point to be considered is whether an "efficient reduction" has been credibly demonstrated.

Since experiment E is a proper repetition of the process described in example 6 of document (2) and the processes described in experiments F and G differ therefrom only by the presence of dimethyl sulfide or diethyl ether, respectively, it cannot be denied that with the experiments submitted at the appeal stage a direct comparison with the closest state of the art, as represented by a disclosed example, was made.

Furthermore, since it follows from the data presented in those experiments that 95%-conversion of the prochiral ketone into the optically active alcohol is only reached after 20 hours of reaction by using the process according to example 6 of document (2), whereas such degree of conversion is already reached after 12 and 15.5 hours of reaction respectively by using the claimed process (experiments F and G), in the Board's view an "efficient reduction", ie an improved conversion rate, has been unambiguously shown with experiments E, F and G. The Board has no reason to query the comparison in respect of their validity for the whole of the components (C) defined in Claim 1.

- 2.3.4 Moreover, the Board cannot follow the Examining Division's argument that it may be derived from decision T 181/82 (supra) that, in order to be valid, a comparison should be made with an example of the closest prior art. In this decision it was only made clear that, for comparative data to be valid, it was not sufficient to make a comparison with "a preferred" representative of the closest prior art, but that comparison should be made with subject-matter possessing maximum similarity with the claimed subject-matter (see points 4 and 5). Even more, the essence of this decision has been

subsequently supplemented by decision T 197/86 (OJ EPO, 1989, 371), according to which the nature of the comparison with the closest state of the art must be such that the effect is convincingly shown to have its origin in the distinguishing feature of the invention (see point 6.1.3 *infra*).

The fact that in the application in suit the claimed process is compared with processes differing from that claimed only by the absence of a component (C) (see examples 1 to 6 in comparison with comparative example 1 and examples 9 to 13 in comparison with comparative examples 2 to 6) is in keeping with the established practice of the Boards of Appeal of considering these comparisons valid for rendering an "efficient reduction" (point 2.3.2 *supra*) credible.

- 2.3.5 From a direct comparison of the percentage conversion according to the claimed processes as described in examples 1 to 6 and 9 to 13 with the percentage conversion according to comparative examples 1 to 6, being representative for the conversion reaction described in document (2), it follows that by the presence of a component (C) the percentage conversion is effectively improved. More particularly, from a comparison of examples 1 to 6 with comparative example 1, it follows that the conversion of a particular prochiral ketone into an optically active alcohol with a reducing agent, obtained by reacting (+)-norephedrine with sodium borohydride, is 71.8% up to 97.4% after 19 to 91 hours when the reducing agent is prepared in the presence of a component (C), namely dimethyl or diethyl sulfide, tetrahydrothiophene, di-*tert*-butyl disulfide, tetrahydrofuran or thiophene, whereas the ketone is converted for only 67.2% after 91 hours when the reducing agent is prepared in the absence of a component (C). Furthermore, such improvement in

conversion may also be derived from a direct comparison of example 9 with comparative example 2 (99.6% and 80.5% after 28 hours), example 10 with comparative example 3 (93.5% and 61.7% after 24 hours), example 11 with comparative example 4 (97.3% and 88.7% after 18.5 hours), example 12 with comparative example 5 (90.5% and 64.1% after 19 hours) and example 13 with comparative example 6 (98.1% and 65.5% after 15 hours).

Moreover, from a direct comparison of those examples and comparative examples, it also follows that an improved conversion may also be obtained by using a different optically active amino alcohol or a different solvent for preparing the boron hydride asymmetric reducing agent, by using a different solvent in the reduction reaction, by reducing a different ketone and by preparing the reducing agent at a different weight ratio of sodium borohydride to the optically active amino alcohol, as it also follows from a direct comparison of experiment J with experiment K (75% and 95% after 98 hours).

Considering all those experimental data, in the Board's view it is convincingly shown that by the claimed process the conversion rate is increased and that such increase has its origin in the presence of component (C). Moreover, it is also convincingly shown that such increase of the conversion rate is also obtained at different process parameters.

- 2.3.6 It remains to be decided whether, in the light of the teachings of documents (1) and (2), a skilled person would have expected that by preparing an asymmetric reducing agent from an optically active amino alcohol and a metal borohydride in the presence of at least one

compound selected from sulfides, cyclic ethers and ethers of mono alcohols an efficient reduction of a prochiral ketone into an optically active alcohol (as defined in point 2.3.2 supra) would be obtained.

2.3.7 Both documents (1) and (2) teach that optically active boron hydride type reducing agents obtained by reacting an optically active amino alcohol with an acid and a metal borohydride are useful asymmetric reducing agents for converting prochiral ketones into optically active alcohols (document (1), page 1, lines 1 to 13, and page 4, line 23, to page 5, line 3, and document (2), page 5, line 24, to page 6, line 9). Additionally, on page 7, line 19, to page 8, line 1, of document (1) and on page 8, lines 14 to 23, of document (2) it is taught that the solvents used in producing the optically active boron hydride type reducing agents are not particularly limited, so long as they do not take part in the reaction. As suitable solvents aromatic hydrocarbons and halogenated hydrocarbons are cited, and dimethyl sulfoxide, diglyme, dimethylformamide and 1,3-dimethyl-2-imidazolidine are mentioned as preferred solvents, since they also dissolve metal borohydrides.

It is true that diethyl ether, tetrahydrofuran and dioxane are said, on page 9, lines 1 to 10, of document (1) and on page 9, line 19, to page 10, line 2, of document (2), to be suitable solvents in the **reduction reaction**, ie in the conversion of a prochiral ketone into an optically active alcohol. However, the use of a sulfide, a cyclic ether or an ether of a mono alcohol in the **preparation of the asymmetric reducing agent** is neither mentioned nor suggested there.

In the Board's judgment, the fact that in both documents it is said that the solvents used in producing the optically active boron hydride type reducing agents are not particularly limited can only be interpreted as meaning that there is no prejudice against the use of particular solvents for carrying out the reduction reaction. However, according to the established practice of the Boards of appeal, in order to demonstrate obviousness, it is necessary to show that the skilled person would have selected one of those solvents with a view to solving the technical problem, as described under point 2.3.2 supra. Therefore, since it could not be expected from the teaching of any of documents (1) and (2), nor from any of the other documents cited in the European search report, that the conversion efficiency of a prochiral ketone into an optically active alcohol would be increased when the asymmetric active amino alcohol is obtained by carrying out the reaction of an optically active amino alcohol with a metal borohydride in the presence of a sulfide, a cyclic ether or an ether of a mono alcohol, a person skilled in the art would not have derived any suggestion from these documents which could assist it in the attempt to solve the stated technical problem.

2.3.8 The Board therefore concludes that the solution of the present technical problem according to Claim 1 was not obvious in the light of the cited state of the art and the common general knowledge.

2.3.9 Claims 2 to 7, which are dependent on Claim 1 and represent preferred embodiments thereof, derive their patentability from that of Claim 1.

2.4 Since the claims according to the main request comply with the requirements of the EPC, a European patent may be granted on the basis of this set of claims.

3. *Auxiliary requests*

In the light of the above findings, there is no need to consider the auxiliary requests.

4. *Description*

The description has been adapted to the claims according to the main request and, like these, satisfies the requirement of Article 123(2) EPC (see point 2.1 above).

Order


For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the Examining Division with the order to grant a patent on the basis of
 - the set of claims according to the main request, filed with letter of 24 May 1996, and
 - pages 1 to 28 of the adapted description filed with letter of 24 May 1996.

The Registrar:


E. Görgmaier

The Chairman:


A. Nuss

