

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HANGSEN INTERNATIONAL GROUP LTD.,
Petitioner,

v.

ZANOPRIMA LIFESCIENCES, LTD.,
Patent Owner.

IPR2023-00503
Patent 10,913,962 B2

Before JEFFREY N. FREDMAN, ZHENYU YANG, and
CYNTHIA M. HARDMAN, *Administrative Patent Judges*.

HARDMAN, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Petitioner Hangsen International Group Ltd. requests *inter partes* review of claims 1–14 (all claims) of U.S. Patent No. 10,913,962 B2 (“the ’962 patent,” Ex. 1001). Paper 2 (“Pet.”). Patent Owner Zanoprima Lifesciences, Ltd. filed a Preliminary Response. Paper 6 (“Prelim. Resp.”). The parties filed an authorized Reply and Sur-reply. Paper 7; Paper 9.

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314 (2018). Upon considering the parties’ arguments and cited evidence, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one claim challenged in the Petition. Accordingly, we do not institute an *inter partes* review.

A. *Real Parties in Interest*

Petitioner identifies “Hangsen International Group Ltd.; Shenzhen Hangsen Star Technology Co., Ltd.; Hangsen E-Cig Technology Co., Ltd.; and Shandong Jincheng Pharmaceutical Chemical Co., Ltd.” as real parties in interest. Pet. 2. Patent Owner identifies itself as the real party in interest. Paper 5 (Patent Owner Mandatory Notices), 1.

B. *Related Matters*

The parties identify *Zanoprima Lifesciences, Ltd. v. Hangsen Int’l Grp. Ltd.*, No. 6:22-cv-00268-ADA (W.D. Tex.) (“the Texas Case”) as a related matter. Pet. 2; Paper 5, 1.

C. *The ’962 Patent (Ex. 1001)*

The ’962 patent, titled “Process of Making (S)-Nicotine,” “relates to a process for synthetically producing (S)-nicotine ([(S)-3-(1-methylpyrrolidin-

2-yl) pyridine]).”¹ Ex. 1001, code (54), 1:5–7. According to the Specification, there is an increasing demand for tobacco replacement products containing nicotine to substitute for traditional tobacco products that result in harmful carcinogenic effects, but “[c]hallenges exist for obtaining nicotine with suitable levels of both enantiomeric purity and chemical purity.” *Id.* at 1:18–27, 1:31–32. The Specification further states that “[n]icotine is optically active, i.e. it may exist in one of two possible enantiomeric forms: (R)-nicotine or (S)-nicotine” and although there are process to obtain racemic mixes of nicotine, “it is acknowledged that (S)nicotine (i.e. [(S)-3-(1-methylpyrrolidin-2-yl) pyridine]) is significantly more active than (R)-nicotine.” *Id.* at 1:32–38.

The Specification states that the “demand in the tobacco industry and in the pharmaceutical field is for nicotine with a high level of enantiomeric purity with respect to the (S) enantiomer.” *Id.* at 1:38–41. The Specification further explains that “(S)-Nicotine may be obtained by extraction from leaves of the tobacco plant” but “when nicotine is obtained this way, it typically has a chemical purity of less than 95% due of the presence of related alkaloid impurities,” which “are of a similar chemical structure to nicotine and consequently are difficult to remove.” *Id.* at 1:61–64, 2:2–4. “(S)-Nicotine may also be obtained by a synthetic process,” but “selectively synthesising (S)-nicotine in preference to the (R) enantiomer with high

¹ The ’962 patent claims priority to a European application filed on November 16, 2018. Ex. 1001, code (30). Petitioner assumes, and Patent Owner does not dispute, that the challenged claims are entitled to claim priority to this date. Pet. 4; *see generally* Prelim. Resp. For purposes of this Decision, we similarly apply a November 16, 2018, priority date.

enantiomeric selectivity whilst also achieving high chemical purity remains a challenge.” *Id.* at 2:7, 2:23–26.

The Specification describes a process for making (S)-nicotine that includes “(i) reducing myosmine with an enzyme with imine reductase activity to form (S)-nornicotine” and “(ii) methylating the (S)-nornicotine formed from step (i) to form (S)-nicotine.” *Id.* at 2:30–35. According to the Specification:

It was surprisingly found that by way of steps (i) and (ii) of this process, where myosmine is used as the starting material, a very high enantiomeric and chemical purity was achieved for (S)-nicotine. This indicates that step (i) is a highly enantiomeric selective synthetic step with preference for the (S) isomer, and that step (ii) is such that this preference is retained in the final nicotine product, whilst also maintaining high chemical purity. This allows the production of (S)-nicotine without having to resort to resolution of a racemic mix.

Id. at 2:36–45.

The Specification explains that “an ‘enzyme with imine reductase activity’ refers to an enzyme capable of asymmetrically reducing an imine group,” and “[i] particular, the enzyme with imine reductase activity used in the process disclosed herein is an enzyme capable of catalysing the conversion of myosmine to (S)-nornicotine.” *Id.* at 3:31–39.

D. The Challenged Claims

Petitioner challenges all 14 claims of the '962 patent. Independent claim 1 is representative and is reproduced below:

1. A process of making (S)-nicotine comprising the steps of:

(i) reducing myosmine with an enzyme with imine reductase activity to form (S)-nornicotine; and

(ii) methylating the (S)-nornicotine formed from step (i) to form (S)-nicotine;

wherein step (ii) is carried out by way of reductive methylation; and

wherein in step (ii) the (S)-nornicotine is reductively methylated, using formaldehyde or a formaldehyde-based compound in the presence of a reductant.

Ex. 1001, 19:59–20:59.

Challenged dependent claims 2–14 depend directly or indirectly from claim 1 and add additional features, including with respect to the claimed reductant (claims 4, 5, 13, 14) and enantiomeric excess of the claimed (S)-nicotine (claim 9), and wherein the process of claim 1 is used for producing a pharmaceutical composition (claims 10, 11) or an electronic cigarette device (claim 12). *Id.* at 20:60–22:16.

E. The Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–14 are unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–14	§ 103	Divi, ² Moody, ³ Enzymicals ⁴
2	6, 12	§ 103	Divi, Moody, Enzymicals, Arnold ⁵
3	7, 8	§ 103	Divi, Moody, Enzymicals, Sheldon ⁶
4	1–14	§ 103	Divi, Moody, Velikogne, ⁷ Wetzl ⁸
5	6, 12	§ 103	Divi, Moody, Velikogne, Wetzl, Arnold
6	7, 8	§ 103	Divi, Moody, Velikogne, Wetzl, Sheldon

² Divi et al., U.S. Patent No. 8,367,837 B2, issued February 5, 2013 (“Divi,” Ex. 1003).

³ Tom Moody, *Biocatalysis: Genes to GMP*, Speciality Chemicals Magazine, 12–14 (January 2016) (“Moody,” Ex. 1004).

⁴ Enzymicals 2017 Portfolio (“Enzymicals,” Ex. 1006). Petitioner asserts that this reference “is a printed publication published and publicly available on the Enzymicals website as early as July 1, 2017.” Pet. 7 (citing Ex. 1007, Declaration of Nathaniel E. Frank-White of the Internet Archive). On this record, Patent Owner does not dispute that Enzymicals qualifies as a prior-art printed publication.

⁵ Arnold, U.S. Patent No. 9,556,142 B2, issued January 31, 2017 (“Arnold,” Ex. 1008).

⁶ Sheldon et al. W.O. Pub. No. 2014/174505 A2, published October 30, 2014 (“Sheldon,” Ex. 1013).

⁷ Stefan Velikogne et al., *Sequence-Based In-silico Discovery, Characterization, and Biocatalytic Application of a Set of Imine Reductases*, 10 ChemCatChem 3236–3246 (2018) (“Velikogne,” Ex. 1011).

⁸ Dennis Wetzl et al., *Expanding the Imine Reductase Toolbox by Exploring the Bacterial Protein-Sequence Space*, 16 ChemBioChem 1749–1756 (2015) (“Wetzl,” Ex. 1009).

Pet. 10. Petitioner support its contentions with, *inter alia*, the Declaration of Jeffrey D. Winkler, Ph.D. Ex. 1002.

II. ANALYSIS

A. *Level of Ordinary Skill in the Art*

We consider the grounds of unpatentability in view of the understanding of a person of ordinary skill in the art (sometimes referred to herein as a “POSITA”) as of November 16, 2018. *See supra* n.1. Petitioner contends that

[a] POSITA with respect to the ’962 Patent would have had a Ph.D. in a relevant field of organic chemistry or biochemistry, with several years of research experience gained during those studies or afterwards in organic synthesis, including chiral synthesis, and the use of enzymes in reactions. Winkler ¶ 51. A POSITA could also include a person with a lesser academic degree, but with several years’ experience sufficient to develop equivalent experience in synthetic organic chemistry, such as in pharmaceutical applications or in the chiral synthesis of compounds with biological activity.

Pet. 13 (citing Ex. 1002 (Winkler Decl.) ¶¶ 51–52). Patent Owner does not dispute Petitioner’s proposal. Prelim. Resp. 5–6.

Because Petitioner’s proposed level of ordinary skill in the art appears to be consistent with the cited prior art and is undisputed on this record, we adopt it for purposes of this Decision.

B. *Claim Construction*

In AIA proceedings we interpret a claim “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b).” 37 C.F.R. § 42.100(b). Under this standard, we construe the claim “in accordance with the ordinary and

customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” *Id.*

Petitioner proposes constructions for two terms: “enzyme with imine reductase activity to form (S)-nornicotine,” recited in claim 1; and “wherein the (S)-nicotine is obtained with an enantiomeric excess of at least 90%, preferably at least 95%, more preferably at least 98%, most preferably at least 99%,” recited in claim 9. Pet. 10–12.

Patent Owner asserts that in the Texas Case, “the Court rejected the very constructions now being presented by Petitioner,” and that “no constructions are necessary at this stage of the proceeding.” Prelim. Resp. 5 (citing Ex. 2001 (Texas Case claim construction order)).

Having reviewed the arguments and evidence of record (including the claim construction order in the Texas Case), we determine that no construction of any claim term is needed to decide whether to institute this Petition. *See Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019) (“The Board is required to construe ‘only those terms . . . that are in controversy, and only to the extent necessary to resolve the controversy.’”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

C. *Principles of Law*

In an *inter partes* review, “the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)). Petitioner ultimately bears the burden of

persuasion to prove unpatentability of each challenged claim by a preponderance of the evidence. 35 U.S.C. § 316(e). This burden never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). The Board may authorize an *inter partes* review if we determine that the information presented in the Petition and Patent Owner's Preliminary Response shows a reasonable likelihood that Petitioner will prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 314(a).

A claim is unpatentable as obvious under 35 U.S.C. § 103 if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which said claimed invention pertains. *See also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved based on underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) any objective indicia of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). An obviousness determination requires finding a reason to combine accompanied by a reasonable expectation of achieving what is claimed in the patent-at-issue. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

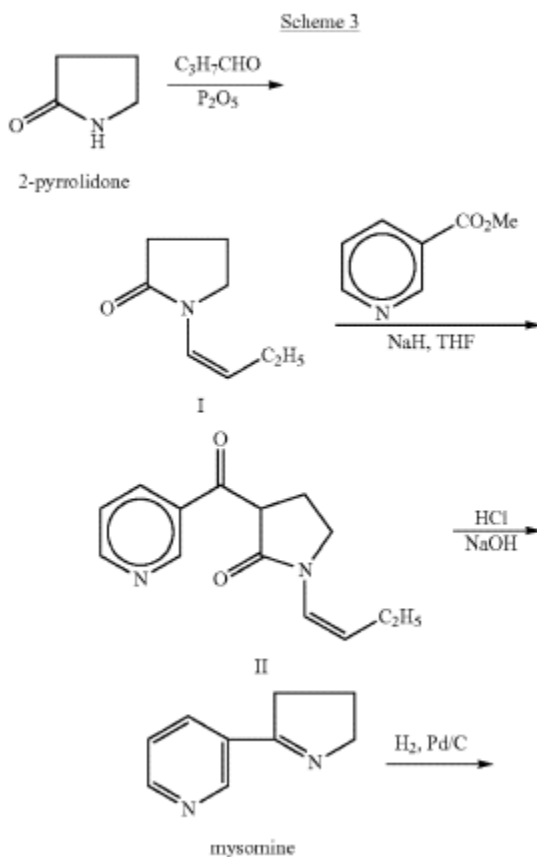
D. Overview of Asserted Prior Art

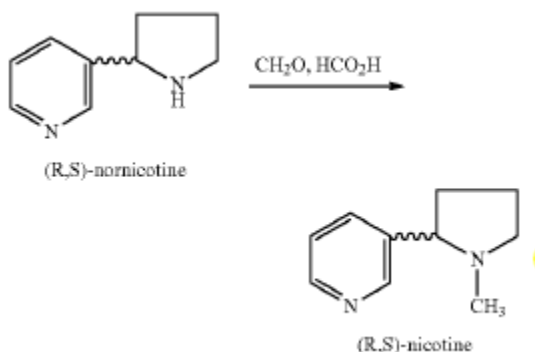
1. Divi (Ex. 1003)

Divi is a U.S. patent titled “Process for the Preparation of (R,S)-Nicotine.” Ex. 1003, code (54). Divi issued on February 5, 2013. *Id.* at

code (45). For purposes of this Decision, we understand that Divi is prior art.

Divi describes “an attractive and economical method for the production of synthetic (S)-nicotine,” comprising the preparation of (R,S)-nicotine through myosmine, followed by “resolution and racemisation of the unwanted (R)-nicotine.” *Id.* at 1:22–25, 1:8–11, 2:16–17. Divi’s scheme for preparing (R,S)-nicotine is outlined below:





Id. at 2:33–3:15.

2. *Moody (Ex. 1004)*

Moody is an article titled “Biocatalysis: Genes to GMP.” Ex. 1004, code (54), ¶ 1. Moody published in January 2016. *Id.* at 12. For purposes of this Decision, we understand that Moody is prior art.

Moody states that there has been “a massive uptake in the synthesis of chiral molecules” due to the application of biocatalysis in chemical processing. *Id.* According to Moody, “[b]iocatalysis has become the workhorse of the chemists’ toolbox for chiral chemistry” and “[e]nzyme processes are now at the epicenter of key drivers in process design, scale-up and economics.” *Id.* Moody explains that “[t]he synthetic power of enzymes is their unequalled selectivity for the chemical reactions they catalyse.” *Id.*

Moody explains that the Almac Group⁹ “can rapidly access specifically built enzyme libraries” to build “tailored catalysts” for a customer’s substrate. *Id.*

⁹ Moody’s author, Tom Moody, is identified as the “head of biocatalysis and radiolabeling at the Almac Group.” Ex. 1004 (Moody), 12.

An example of this is depicted in Moody's Figure 3, reproduced below.

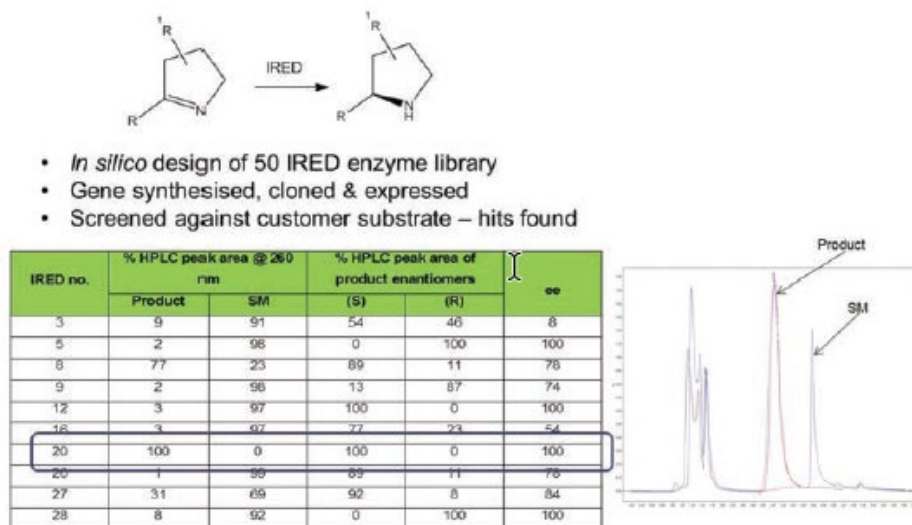


Figure 3 – IRED enzyme application

Moody explains that Figure 3 “involved an imine reductase (IRED) project where Almac specifically designed 50 IREDS for the enantioselective reduction of the imine,” “resulting in the identification of an active and selective IRED catalyst.” *Id.* at 12–13.

3. *Enzymicals (Ex. 1006)*

Enzymicals is a brochure describing chemicals, enzymes, and services available from the Enzymicals company. *See generally* Ex. 1006. Petitioner asserts, and on this record Patent Owner does not dispute, that Enzymicals was publicly available as of January 2017. Pet. 17; Ex. 1007. For purposes of this Decision, we understand that Enzymicals is prior art.

Enzymicals states that imine reductases are available from the company, including two imine reductases that are “(R)-selective towards the standard substrate 2-Methyl-1-pyrroline” and two imine reductases that are

“(S)-selective towards the standard substrate 2-Methyl-1-pyrroline,” as well as a screening kit including all four of these imine reductases. Ex. 1007, 9, 38, 40. Enzymicals further describes an “[i]n-house enzyme screening” service wherein Enzymicals will “screen your substrate to find out the most suitable enzyme for your desired reaction.” *Id.* at 48. Enzymicals additionally states that enzyme variants are available, specifically “[m]utants with enhanced substrate specificity and/or increased stereoselectivity towards appropriate substrates.” *Id.* at 52.

4. *Arnold (Ex. 1008)*

Arnold, a U.S. patent titled “Process for the Preparation of (R,S)-Nicotine,” relates to “the large scale manufacturing of pure (R,S)-nicotine, and its use in vapor for treatment of tobacco smoking cessation and/or recreational use.” Ex. 1008, code (54), 1:15–18. Arnold issued on January 31, 2017. *Id.* at code (45). For purposes of this Decision, we understand that Arnold is prior art.

Arnold describes a scheme that includes mixing a nicotinate ester with an N-vinyllogous-2-pyrrolidinone, using that mixture to form crude myosamine,¹⁰ reducing the myosamine to form crude nornicotine, and reacting the crude nornicotine with a mixture of water, formic acid, and formaldehyde to produce R,S-nicotine, which is subsequently purified. *Id.* at 2:28–3:17, 5:9–16, 5:36–38, 6:1–18.

¹⁰ Myosamine as referenced in Arnold is the same compound as myosmine referenced in Divi. *Compare* Ex. 1008 (Arnold), 2:45–52 (compound 3), with Ex. 1003 (Divi), 2:60–65 (compound II (the label in this figure misspells the compound as mysomine)).

5. *Sheldon (Ex. 1013)*

Sheldon, a published international patent application, is titled “A Process for the Preparation of Nicotine Comprising the Enzymatic Reduction of 4-(Methylamino)-1-(Pyridin-3-YL) Butan-1-One.” Ex. 1013, code (54), 1:15–18. Sheldon was published on October 30, 2014. *Id.* at code (43). For purposes of this Decision, we understand that Sheldon is prior art.

Sheldon describes “a process for the preparation of nicotine comprising the enzymatic reduction of 4-(methylamino)-1-(pyridin-3-yl)butan-1-one” (“pseudooxynicotine”). *Id.* at 2. Sheldon further describes “that nicotine can be prepared directly from pseudooxynicotine by the enzymatic reduction of pseudooxynicotine using imine reductase enzymes,” such as those “commercially available, for example, from Enzymicals AG (Greifswald, Germany).” *Id.* at 18. Sheldon describes dissolving pseudooxynicotine in a suitable solvent, preferably water, and “as known in the art, an aqueous salt solution or a buffer may be used as needed in order to avoid denaturation of the reductase enzymes.” *Id.* at 21.

6. *Velikogne (Ex. 1011)*

Velikogne is an article titled “Sequence-Based *In-silico* Discovery, Characterisation, and Biocatalytic Application of a Set of Imine Reductases.” Ex. 1011, 3236. Petitioner asserts, and on this record Patent Owner does not dispute, that Velikogne was publicly available as of June 28, 2018. Pet. 18; Ex. 1010 ¶¶ 54–63. For purposes of this Decision, we understand that Velikogne is prior art.

According to Velikogne, “a large number of imine reductases [“IREDs”] have been identified and heterologously expressed, and their

substrate scope, their kinetic properties, their three-dimensional structure and their applicability in preparative-scale reactions have been investigated.” Ex. 1011, 3236. Velikogne “report[s] the sequence-based *in-silico* discovery and characterisation of eight novel imine reductases along with the investigation of six known IREDs,” and “the application of these enzymes in the asymmetric reduction of cyclic imines.” *Id.* at 3237. More specifically, Velikogne describes the determination of stereoselectivity for fourteen IREDs (A–N) and their activity towards ten imines (1a–k). *Id.* at 3239. The results are shown in Velikogne’s Figure 3, which we reproduce below.

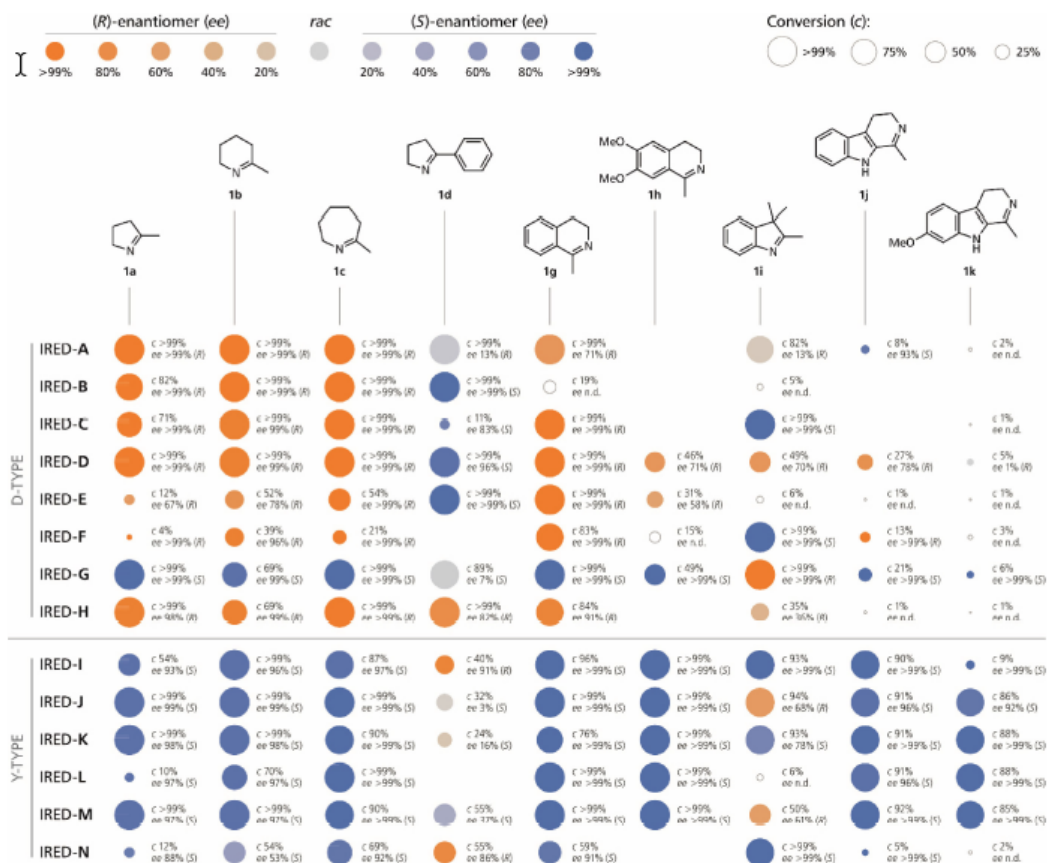


Figure 3. Conversions (c) and optical purities (ee) observed in the reduction of imines 1a–d and 1g–k by the investigated D-type and Y-type IREDs. *Reaction conditions:* Substrate 1 (10 mM), NADP⁺ (1 mM), IRED (2 mg/mL crude preparation), Lb-ADH (2 mg/mL crude preparation), Tris-HCl buffer (100 mM, pH 7.5; IREDs A–E, I–M) or potassium phosphate buffer (100 mM, pH 6.0; IREDs F–H, N), 2-PrOH (5% v/v), 30 °C, 24 h. Empty circles indicate products whose ee was not determined, and blank spaces indicate reactions in which no product formation was detected.

Id. at 3240. Velikogne states: “As shown in Figure 3, high conversions and excellent optical purities were attained in many of the reactions and the observed stereoselectivities largely follow the expected patterns, with the previously discussed exception of the (S)-selective D-type IRED-G.” *Id.* at 3239.

7. *Wetzel (Ex. 1009)*

Wetzel, an article titled “Expanding the Imine Reductase Toolbox by Exploring the Bacterial Protein-Sequence Space,” relates to the characterization of new imine reductases. Ex. 1011, 1749. Petitioner asserts, and on this record Patent Owner does not dispute, that Wetzel was publicly available as of September 23, 2015. Pet. 19; Ex. 1010 ¶¶ 64–73. For purposes of this Decision, we understand that Wetzel is prior art.

Wetzel describes a study of several novel IREDs, wherein the IREDs were screened against a set of “model substrates compris[ing] different monocyclic . . . and bicyclic aliphatic imines . . . as well as aryl substrates with a benzylic imine functional group” “using a deep-well based screening method that allowed the screening of one substrate against the entire library.” Ex. 1009, 1750. According to Wetzel, “10 of the 13 new IRED candidates were active against most of the screened substrates, while only a few candidates seemed to have a rather limited substrate scope with low conversions under the screened conditions.” *Id.* “The vast majority of the tested IRED candidates displayed good conversions (> 90 %) against nearly all of the tested substrates as well as good to excellent enantioselectivities, often yielding the corresponding product with an enantiomeric excess > 90 %.” *Id.*

E. Ground 1: Alleged Obviousness Over Divi, Moody, and Enzymicals

Petitioner asserts that claims 1–14 are unpatentable as obvious over Divi, Moody, and Enzymicals. Pet. 20–41. Patent Owner opposes. *See generally* Prelim. Resp. 8–19. For the reasons discussed below, on this record we determine that Petitioner has not shown a reasonable likelihood of establishing that at least one of the challenged claims is unpatentable as obvious over Divi, Moody, and Enzymicals.

We begin by summarizing Petitioner’s arguments, focusing on the key claim limitations and arguments most relevant to our analysis. Regarding the preamble (“A process for making (S)-nicotine comprising the steps of:”), Petitioner asserts that Divi teaches “an attractive and economical method for the production of synthetic (S)-nicotine,” wherein (1) myosmine is reduced to form (R,S)-nornicotine; (2) the (R,S)-nornicotine is methylated to form racemic (R,S)-nicotine; and (3) the “unwanted” (R)-nicotine is separated from the racemic (R,S)-nicotine mixture in a resolution step, resulting in (S)-nicotine. Pet. 13–14 (citing, *e.g.*, Ex. 1003 (Divi), 2:21–25, 2:32–3:19). Petitioner contends that “[a] POSITA would have looked at the reaction disclosed in Divi as a logical starting point, while recognizing that avoiding a resolution step would further improve the reaction.” *Id.* at 21 (citing Ex. 1002 (Winkler Decl.) ¶¶ 119–20).

Regarding claim 1 step (i) (“reducing myosmine with an enzyme with imine reductase activity to form (S)-nornicotine;”), Petitioner asserts that although in Divi’s process, myosmine is reduced in an achiral reaction to form racemic nornicotine, a person of ordinary skill in the art would have known that imine reductases could be used to reduce imines (like myosmine)

to amines (like nornicotine) asymmetrically. *Id.* at 22, 24 (citing, *e.g.*, Ex. 1002 (Winkler Decl.) ¶¶ 122, 129). Petitioner argues that a person of ordinary skill in the art would have known of commercially-available services, *e.g.*, from Enzymicals and Almac (as discussed in Moody), that could screen for and/or design imine reductases suitable to asymmetrically reduce a given imine to a chiral amine. *See, e.g., id.* at 23–25 (citing, *e.g.*, Ex. 1006 (Enzymicals), 38–40; Ex. 1004 (Moody), 12, Fig. 3; Ex. 1002 (Winkler Decl.) ¶¶ 129, 132). Petitioner argues that “[a] POSITA would have been motivated to screen imine reductases using Enzymicals or Almac to find an imine reductase catalyzing the asymmetric reduction of myosmine to (S)-nornicotine.” *Id.* at 25; *see also id.* at 27 (“[A] POSITA would have understood from Moody and Enzymicals that commercial services could analyze a ‘customer substrate’ imine (such as myosmine), build a custom enzyme screen of imine reductases targeting the reduction of myosmine, and identify an imine reductase ‘for the enantioselective reduction of the imine.’”) (quoting Ex. 1004 (Moody), 12; citing Ex. 1002 (Winkler Decl.) ¶ 136).

Petitioner argues that “[a] POSITA would have had a reasonable expectation of success that Enzymicals or Almac would identify an imine reductase to reduce myosmine to (S)-nornicotine asymmetrically.” Pet. 28 (citing Ex. 1002 (Winkler Decl.) ¶ 138). This is because Enzymicals sold a screening kit of four imine reductases, and Enzymicals and Almac offered screening services using known and custom-designed imine reductases. *Id.* (citing, *e.g.*, Ex. 1006 (Enzymicals), 52; Ex. 1004 (Moody), 12; Ex. 1002 (Winkler Decl.) ¶¶ 139–40). Petitioner also relies on Moody’s disclosure that Almac had successfully identified “an imine reductase from an enzyme

screen to reduce a customer-supplied target imine to the (s)-amine with 100% enantiomeric excess.” *Id.* at 28–29 (citing Ex. 1004 (Moody), 12, Fig. 3; Ex. 1002 (Winkler Decl.) ¶ 140).

Patent Owner argues that Petitioner fails to show that one of ordinary skill in the art would have had a reason to modify Divi with Moody and Enzymicals, and a reasonable expectation of success in doing so. Prelim. Resp. 8–19. We agree with Patent Owner.

Divi teaches a non-enantioselective synthesis of racemic nicotine, followed by a resolution and racemization step to separate (S)-nicotine from (R)-nicotine. Ex. 1003 (Divi), 2:21–25; Pet. 14, 21; Prelim. Resp. 8. Petitioner asserts that a person of ordinary skill in the art would have modified Divi’s process because “avoiding a resolution step would further improve the reaction.” Pet. 21 (citing Ex. 1002 (Winkler Decl.) ¶¶ 119–20); *see also id.* at 14 (citing Ex. 1002 (Winkler Decl.) ¶ 94).

Petitioner’s only support for its assertion that a person of ordinary skill in the art would have modified Divi’s process to “avoid[] a resolution step” is a citation to an identical, conclusory statement by Dr. Winkler. *See* Pet. 14, 21; Ex. 1002 (Winkler Decl.) ¶¶ 94, 119–20. We agree with Patent Owner that Dr. Winkler’s testimony is entitled to little or no weight, because it does not disclose the underlying facts or data on which the opinion is based. *See* 37 C.F.R. § 42.65(a); *Xerox Corp. v. Bytemark*, IPR2022-00624, Paper 9, 15 (PTAB 2023) (precedential) (explaining that declaration testimony that “is conclusory and unsupported” and which “adds little to the conclusory assertion for which it is offered to support . . . is entitled to little weight”). Obviousness arguments “cannot be sustained by mere conclusory statements; instead, there must be some articulated

reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). On this record, Petitioner and Dr. Winkler fail to adequately explain why a person of ordinary skill in the art would have wanted to modify Divi’s process to “avoid[] a resolution step,” or why converting Divi’s process to an enantioselective synthesis would have “improve[d] the reaction,” particularly in view of Divi’s teaching that “enantioselective synthesis is too expensive on an industrial scale.” Ex. 1003 (Divi), 2:8–11; *see also id.* at 1:64–2:4 (discussing expense of chiral intermediates and catalysts and their lack of suitability for industrial production).

Even if we agree that Petitioner had established a reason to modify Divi’s process to use an imine reductase to reduce myosmine to (S)-nornicotine asymmetrically, on this record we find that Petitioner has not demonstrated a reasonable likelihood that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed subject matter. Petitioner asserts that “[a] POSITA would have had a reasonable expectation of success that Enzymicals or Almac would identify an imine reductase to reduce myosmine to (S)-nornicotine asymmetrically,” given that Enzymicals sold a screening kit and offered mutant enzymes. Pet. 28 (citing Ex. 1002 (Winkler Decl.) ¶ 138). Petitioner, however, fails to adequately explain how the mere commercial availability of a screening kit and enzyme screening and engineering services would have led a person of ordinary skill in the art to reasonably expect that an appropriate imine reductase would be identified. We agree with Patent Owner that “Petitioner presents no evidence a POSITA would expect that Enzymical’s screening kit of four enzymes—two of which are selective against the opposite

stereoisomer as the other two—would lead to the successful reduction of myosmine to (S)-nornicotine.” Prelim. Resp. 17. We also agree with Patent Owner that “Enzymicals does not disclose any specific details of its enzyme screening service or mutant enzymes that would inform a POSITA of the critical parameters necessary to determine whether there is a reasonable expectation of success when used with undisclosed substrates, such as myosmine.” *Id.*

Petitioner cites Moody’s disclosure that Almac had successfully identified an imine reductase for a customer-supplied target. Pet. 28–29 (citing Ex. 1002 (Winkler Decl.) ¶ 140; Ex. 1004 (Moody), 12, Fig. 3). Unlike Enzymicals, Moody at least indicates the successful identification of an imine reductase for at least one substrate. But Moody neither identifies that substrate nor provides any details about it, such that a person of ordinary skill in the art could have evaluated whether the success demonstrated for that unidentified substrate would have been reasonably likely to carry over to myosmine. *See also* Prelim. Resp. 17–18 (“[L]ike Enzymicals, Moody does not disclose the details of how it designs its enzyme screen such that it would inform a POSITA of the critical parameters necessary to determine whether there would be a reasonable expectation of success when used with undisclosed substrates.”). In other words, Moody does not indicate—and Petitioner does not explain—how typical or widely applicable Moody’s results are against other substrates, including myosmine.

Patent Owner correctly states that “Petitioner’s modification of Divi with both Moody and Enzymicals presents four different approaches for identifying an imine reductase capable of reducing myosmine to (S)-nornicotine—the screening kit, the in-house screening service, the mutant

enzymes disclosed in Enzymicals, and the *in silico* enzyme design and screening service disclosed in Moody.” Prelim. Resp. 18. We agree with Patent Owner that “[t]his reliance on four distinct and separate approaches illustrates that Petitioner is proposing the use of trial and error without any discernable direction or guidance disclosed in the references themselves and is, instead, using hindsight to cull selective disclosures to arrive at the asserted combination.” Prelim. Resp. 18. “[T]o have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of the numerous possible choices until one possibly arrived at a successful result, where the prior art gave no indication of which parameters were critical or no direction as to which of the many possible choices is likely to be successful.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007) (quoting *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006)); *see also* Prelim. Resp. 15–16.

Petitioner’s proposed trial-and-error approach is exemplified in Moody, where “out of the 50 imine reductases that were designed to target the specific, unidentified imine, only one imine reductase showed the reduction of the imine to the (S)-isomer with high activity and selectivity.” Prelim. Resp. 18 (citing Ex. 1004 (Moody), 13, Fig. 3). On this record, we agree with Patent Owner that “[t]hese facts indicate that Almac’s *in silico* enzyme design had not identified the critical parameters for success and was simply varying all the parameters to hopefully identify a hit, which does not establish a reasonable expectation of success absent impermissible hindsight.” *Id.*

On this record, Petitioner has not established a reasonable likelihood of demonstrating that claim 1 would have been obvious over Divi, Moody,

and Enzymicals. Dependent claims 2–14 incorporate all of the limitations of independent claim 1. Petitioner’s arguments and evidence for these dependent claims do not remedy the deficiencies discussed above for claim 1. *See generally* Pet. 31–41; Prelim. Resp. 19. Accordingly, Petitioner has not demonstrated a reasonable likelihood of prevailing on Ground 1.

F. Ground 4: Alleged Obviousness Over Divi, Moody, Velikogne, and Wetzl

Petitioner asserts that claims 1–14 are unpatentable as obvious over Divi, Moody, Velikogne, and Wetzl. Pet. 46–70. Patent Owner opposes. *See generally* Prelim. Resp. 20–30. For the reasons discussed below, on this record we determine that Petitioner has not shown a reasonable likelihood of establishing that at least one of the challenged claims is unpatentable as obvious over Divi, Moody, Velikogne, and Wetzl.

Similar to its arguments in Ground 1, Petitioner contends that “[a] POSITA would have looked at the reaction disclosed in Divi as a logical starting point, while recognizing that avoiding a resolution step would further improve the reaction,” and “would have recognized that the Divi reaction provided an opportunity for a stereoselective reaction where myosmine is reduced to nornicotine.” Pet. 47 (citing Ex. 1002 (Winkler Decl.) ¶¶ 218–19), 52 (citing Ex. 1002 (Winkler Decl.) ¶ 235). Petitioner also relies on Moody in the same way it relied on Moody for Ground 1. *See, e.g., id.* at 48, 51 (“Moody disclosed the commercial availability of custom enzyme screens for a customer’s substrates.”), 54 (“A POSITA would have been motivated to use Almac to identify an imine reductase capable of

reducing myosmine to (S)-nornicotine and use that imine reductase to catalyze the asymmetric reduction of myosmine to (S)-nornicotine.”).

In Ground 4, Petitioner adds two new references, Wetzl and Velikogne, both of which report on screening assays of imine reductases. *See, e.g., id.* at 48–49. According to Petitioner, “Wetzl screened about 20 imine reductases and found that the ‘vast majority of the tested IRED candidates displayed good conversions (>90%) against nearly all of the tested substrates as well as good to excellent enantioselectivities, often yielding the corresponding product with an enantiomeric excess > 90%.” *Id.* at 49 (quoting Ex. 1009 (Wetzl), 1750). Similarly, “Velikogne demonstrated that a screen of 14 imine reductases reduced a broad panel of imines to their corresponding amines.” *Id.* at 49–50 (citing Ex. 1011 (Velikogne), 3240). Petitioner asserts that “[a] POSITA would have understood from Velikogne’s imine reductase screen that most imine reductases reduce a wide range of imines,” and that “on the relatively small imine reductase screen, every single screened imine was reduced by at least two imine reductases to the corresponding (S)-amine with at least 99% excess.” *Id.* at 50–51 (citing Ex. 1002 (Winkler Decl.) ¶ 231).

On this record we find that Petitioner has not demonstrated a reasonable likelihood of establishing the required reasonable expectation of success. Petitioner asserts that “[a] POSITA would have had a reasonable expectation of success that a screen would identify an imine reductase to reduce myosmine to (S)-nornicotine asymmetrically.” Pet. 54 (citing Ex. 1002 (Winkler Decl.) ¶ 241). Petitioner points to Moody’s discussion of how Almac performed a screen that identified an imine reductase for a customer-provided substrate, as well as Velikogne and Wetzl’s successful

screens, and asserts that these prior successes would have provided a person of ordinary skill in the art a reasonable expectation of identifying an imine reductase that would selectively reduce myosmine to (S)-nornicotine.

Pet. 55–58; Ex. 1002 (Winkler Decl.) ¶¶ 243–45.

Petitioner, however, does not adequately explain how success with the substrates in Moody, Velikogne, and/or Wetzl would have provided a person of ordinary skill in the art with a reasonable expectation of success of identifying an imine reductase that would be reasonably likely to reduce myosmine to (S)-nornicotine. Moody neither identifies its substrate, nor discloses the details of how it designs its enzyme screen such that it would have informed a person of ordinary skill in the art of the critical parameters necessary to identify a suitable imine reductase. Prelim. Resp. 27–28; *Pfizer, Inc.*, 480 F.3d at 1365.

Petitioner also relies on Velikogne, which “screened a total of 14 imine reductases against 11 imines.” Prelim. Resp. 28 (citing Ex. 1011 (Velikogne) Table 1, Fig. 2). Although Petitioner touts that “Velikogne’s screen resulted in every single screened imine substrate being selectively reduced to the corresponding (S)-amine by multiple imine reductases with at least 99% enantiomeric excess” (Pet. 57), we agree with Patent Owner that “[t]here are far more imines (thousands if not millions) that were not evaluated by Velikogne,” including myosmine. Prelim. Resp. 28. Petitioner neither makes any parallels between Velikogne’s tested imines and myosmine to identify the critical parameters for success, nor “point[s] to any [other] evidence that Velikogne informs a POSITA of the critical parameters necessary to determine whether there would be a reasonable expectation of

success for the reduction of myosmine to (S)-nornicotine.” Prelim. Resp. 29.

Petitioner asserts that “Wetzel disclosed that ‘[t]he vast majority of the tested IRED candidates displayed good conversions (>90%) against nearly all of the tested substrates.’” Pet. 56. As an initial matter, it is unclear whether Wetzel reports any asymmetric conversion for one third of the tested imines (substrates 7, 9, and 11). *See* Ex. 1009 (Wetzel), Table 2 (reporting that the enantiomeric excess of formed product was not determined for these substrates); Prelim. Resp. 29. But even if Wetzel had reported “good conversions (>90%)” for all (or even two-thirds) of the tested substrates, we agree with Patent Owner that Petitioner does not present any evidence to explain why Wetzel’s results would have led a person of ordinary skill “to have a reasonable expectation of success that Moody’s *in silico* enzyme design and screen would identify a[n] imine reductase that reduces myosmine—a completely different compound—to (S)-nornicotine.” Prelim. Resp. 29.

In short, Petitioner relies on a person of ordinary skill in the art commissioning a screen to identify an appropriate imine reductase, but does not explain how or whether the references identify the critical parameters for success. Instead, Petitioner merely suggests simply varying all the parameters—and apparently trying all known imine reductases, and/or engineering a custom reductase—to hopefully identify a hit. This is not sufficient to establish a reasonable likelihood of demonstrating obviousness. *Pfizer, Inc.*, 480 F.3d at 1365. Moreover, Petitioner’s statement that “[a] POSITA replicating Wetzel’s exact panel of imine reductases would have discovered a working imine reductase” is infected with impermissible

hindsight, because it fails to demonstrate a reasonable expectation of success grounded in what a person of ordinary skill in the art would have known prior to the challenged patent's disclosure. Pet. 56; Prelim. Resp. 30.

On this record, Petitioner has not established a reasonable likelihood of demonstrating that claim 1 would have been obvious over Divi, Moody, Velikogne, and Wetzl. Dependent claims 2–14 incorporate all of the limitations of independent claim 1. Petitioner's arguments and evidence for these dependent claims do not remedy the deficiencies discussed above for claim 1. *See generally* Pet. 59–70; Prelim. Resp. 30. Accordingly, Petitioner has not demonstrated a reasonable likelihood of prevailing on Ground 4.

G. Remaining Grounds

Petitioner asserts that (a) claims 6 and 12 are unpatentable as obvious over Divi, Moody, Enzymicals, and Arnold (Ground 2); and (b) claims 7 and 8 are unpatentable as obvious over Divi, Moody, Enzymicals, and Sheldon (Ground 3). Pet. 41–46. Petitioner's arguments and evidence for these additional grounds rely on its arguments for Ground 1, and do not remedy the deficiencies discussed above for Ground 1. *See id.* at 41, 43, 44 (incorporating arguments made in Petition for Ground 1); *supra* Section II.F; Prelim. Resp. 19–20. Accordingly, Petitioner has not demonstrated a reasonable likelihood of prevailing on Grounds 2 and 3.

Petitioner additionally asserts that (c) claims 6 and 12 are unpatentable as obvious over Divi, Moody, Velikogne, Wetzl, and Arnold (Ground 5); and (d) claims 7 and 8 are unpatentable as obvious over Divi, Moody, Velikogne, Wetzl, and Sheldon (Ground 6). Pet. 71–76. Petitioner's arguments and evidence for these additional grounds do not

remedy the deficiencies discussed above for Ground 4. *See id.* at 71, 73, 74, (incorporating arguments made in Petition for Ground 4); *supra* Section II.G; Prelim. Resp. 31. Accordingly, Petitioner has not demonstrated a reasonable likelihood of prevailing on Grounds 5 and 6.

III. CONCLUSION

After considering the evidence and arguments of record, we determine that Petitioner has not demonstrated a reasonable likelihood of prevailing with respect to any claim challenged in the Petition.¹¹ Accordingly, we do not institute an *inter partes* review.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied*, and no trial is instituted.

¹¹ Because we deny the Petition on the merits, we do not reach Patent Owner's argument for discretionary denial under 35 U.S.C. § 314. Prelim. Resp. 31–37.

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