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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. **05.027.433**
Solicitud de patente a nombre de **NOVARTIS AG**

Yo, DILIA RODRIGUEZ D'ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad **NOVARTIS AG** domiciliada en Basilea, Suiza, solicitante de la patente de la referencia, *interpongo recurso de reposición* contra la resolución No. 23612 del día 30 de abril de 2010, expedida por el Superintendente de Industria y Comercio, por medio de la cual se niega el privilegio de patente para la solicitud contenida en el expediente de la referencia.

1. FUNDAMENTOS DEL RECURSO

1.1 Mi mandante se permite manifestar a ese despacho que se reafirma en todos y cada uno de los argumentos que hacen parte integrante de la respuesta al oficio de fondo No. 16158 notificado por fijación en lista el día 19 de diciembre de 2008, presentada ante ese despacho el día 16 de marzo de 2009, y al oficio 5681 notificado por fijación en lista el día 15 de mayo de 2009, presentada ante ese despacho el día 12 de agosto de 2009.

1.2 El indebido análisis del Nivel Inventivo

En su resolución el examinador insiste en objetar el nivel inventivo de la presente solicitud, argumentando que para el técnico con habilidad ordinaria en la materia habría sido obvio derivar la invención en estudio a partir de lo dicho por las anterioridades D1 a D3. Al respecto el solicitante quisiera hacer los siguientes comentarios:

Ninguno de los documentos citados por el examinador enseña o sugiere al técnico con habilidad ordinaria en la materia las condiciones necesarias para obtener valsartan en un medio básico. De hecho, D1 y D2 sugieren llevar a cabo las reacciones de aminación reductiva en un proceso aparte de la reacción principal. Aunque el examinador tiene razón en cuanto a las condiciones de pH y presencia de una fuente de protones capaz de garantizar la reacción, para el técnico con habilidad ordinaria en la materia no es fácil derivar a partir de las condiciones de la afinación reductiva de D1, D2 o D3 un proceso que incorpore

dicha etapa de aminación reductiva sin que sea necesario implementar un proceso aparte. Esto, de por si, es un efecto sorprendente de la presente invención, ya que el arte previo no menciona nada al respecto.

Es claro que todas las reacciones de los procesos de D1 y D2 se llevan a cabo en un medio ácido y que la afinación reductiva se lleva a cabo en una reacción aparte, en un medio básico. Para el técnico con habilidad ordinaria en la materia no sería obvio simplemente a partir de sus conocimientos, los cambios necesarios para permitir que la totalidad de la reacción se lleve a cabo en medio básico, particularmente porque ninguno de los documentos citados enseña o sugiere cuáles deben ser estos cambios.

La presente solicitud enseña un proceso para obtener Valsartan y una serie de compuestos intermedios útiles en procesos similares. **Todo el proceso se lleva a cabo bajo condiciones básicas**, lo cual hace necesario incorporar otras condiciones, otros reactivos y otros grupos protectores que no se mencionan ni sugieren en el estado de la técnica.

El examinador parece enfocarse esencialmente en las fórmulas de los intermedios y en el proceso de afinación reductiva, sin tener en cuenta las condiciones totales del proceso, que también forman parte de la materia reclamada por el solicitante. Establecer que para el técnico con habilidad ordinaria en la materia sería obvio hacer los cambios necesarios para pasar de un proceso de dos etapas, una en medio ácido y otra en medio básico, a un proceso de una sola etapa que se lleva a cabo **totalmente en medio básico** no significa que sea cierto. El arte previo no enseña ni sugiere como llevar a cabo las demás reacciones en un medio ácido y el examinador no proporciona evidencia alguna que demuestre que dicho conocimiento ya formaba parte de los conocimientos propios del técnico con habilidad ordinaria en la materia. En este sentido el artículo 18 de la Decisión 486 señala que *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*, pudiéndose concluir que el supuesto de la norma indica que corresponde al examinador probar con sus argumentos que los aspectos incluidos en la invención son conocimientos propios de un técnico con conocimientos medios en la materia al decir el artículo que la invención tendrá nivel inventivo si no resulta obvia y si no se ha derivado de manera evidente del estado de la técnica. Estos hechos deben demostrarse y sin embargo como aquí lo indicamos estos supuestos de la norma no se dan de forma negativa en este caso concreto ya que el arte previo no tiene los conocimientos propios que demuestren la falta de nivel inventivo de esta invención.

De acuerdo con la presente invención, sorprendentemente se ha encontrado que

una amina quiral de fórmula (IIc) para la síntesis de valsartan puede prepararse mediante la reacción de aminación reductiva bajo condiciones básicas **sin racemización**. Tal amina quiral es el producto de un paso de afinación reductiva, en donde un aminoácido quiral, de fórmula (IIb), reacciona con un aldehído, de fórmula (IIa), el cual es luego reducido. Es bien sabido por el técnico con habilidad ordinaria en la materia que **los aminoácidos quirales pueden racemizarse bajo condiciones básicas** y también es bien conocido que **las iminas (también conocidas como bases de Schiff) de aminoácidos quirales pueden racemizarse**. Para sustentar esto aún más, el solicitante adjunta un artículo de Ebbers, E. J. Tetrahedron (Ver anexo 1). Dicho anexo 1 es una revisión de la racemización de compuestos orgánicos ópticamente activos, en particular, se hace referencia a las secciones 4.2 y 4.4. del mismo.

Como se describe en la sección 4.2.1, es generalmente aceptado que los aminoácidos quirales pueden racemizarse bajo condiciones básicas. Similarmente, se muestra en la sección 4.4 que los aminoácidos pueden racemizarse por medio de las bases de Schiff (en otras palabras, mediante las iminas del grupo amino de los aminoácidos).

Como se muestra en el esquema presentado en el anexo 2, también adjunto a la presente, el intermedio imina quiral formado durante el paso imitación reductiva puede racemizarse por dos rutas alternativas bajo condiciones básicas. La primera alternativa que lleva a la racemización del intermedio de imina quiral involucra la abstracción del α-hidrógeno, por la base presente en el medio de reacción para proporcionar un carbanión plano, el cual también existe en el enolato correspondiente, como se muestra en el anexo 2. La protonación subsecuente del enolato plano puede ocurrir desde cualquier cara del doble enlace y esto lleva a los enantiómeros y la racemización resultante. La segunda alternativa que lleva a la racemización involucra un cambio tautomérico reversible del α-hidrógeno y el doble enlace de la imina. En este segundo mecanismo, el cambio del doble enlace de la imina resulta en una pérdida de la quiralidad ya que se pierde el centro quiral al ocurrir el cambio a la imina conjugada. El cambio de portones subsiguiente que lleva a la imina no conjugada puede también tener lugar en cualquier lado del doble enlace y conlleva a los enantiómeros, lo cual también resulta en la racemización.

La naturaleza de los sustituyentes R y R3, como se muestra en el anexo 2, puede afectar las tasas de racemización en cada uno de los dos mecanismos descritos arriba. Para sustentar aún más esta afirmación, se hace referencia al segundo párrafo de la página 9433 del anexo 1, el cual enumera los factores que influencian y afectan la tasa de racemización.

El examinador argumenta que no es posible determinar un efecto sorprendente entre la presente reacción propuesta y las que se enseñan en el arte previo. El proceso reclamado es económicamente ventajoso para la fabricación comercial de producto conocido como Diovan ® (en otras palabras, valsartan). La síntesis del cualquier producto farmacéutico comercial, como el valsartan, que comprende un paso donde ocurre racemización es económicamente poco atractivo porque la racemización siempre resulta en **una reacción secundaria que reduce la cantidad de producto de interés y conlleva a la necesidad de implementar etapas de purificación adicionales** para remover los enantiomeros indeseables.

Por lo tanto, si la preparación sintética de una droga incluye un paso en donde hay racemización, se requieren pasos adicionales para obtener el producto comercial enantioméricamente puro, lo cual implica más reactivos, solventes y equipos adicionales con la intervención y asistencia de un operario humano lo que genera costos adicionales. Además, como es bien sabido en el campo técnico correspondiente, el rendimiento total de la ruta sintética disminuye a medida que se incrementa el número de pasos de la síntesis y/o la purificación, puesto que el rendimiento de ningún proceso de purificación es ni tan siquiera cercano al 100%.

En consecuencia, la ocurrencia de la racemización en un paso de la síntesis también ayuda a reducir el rendimiento total del proceso de fabricación. El hecho que el paso de afinación reductiva bajo condiciones básicas ocurra sin racemización lleva no solo a un incremento en el rendimiento del paso mismo (ya que no hay una reacción lateral que lleva a un enatiomero indeseable), sino también a un incremento del rendimiento total del proceso de fabricación (ya que no se requieren pasos adicionales para remover el enantiomero). Ambas son propiedades altamente deseables para los procesos de fabricación a una escala industrial, particularmente cuando se fabrican productos farmacéuticos. La demanda de un alto rendimiento y una selectividad enantiomérica en la preparación industrial de productos ópticamente activos, en particular productos farmacéuticos, se resalta por ejemplo en el último párrafo de la página 9465 del anexo 1.

En cuanto a la anterioridad D1, la misma presenta dos variaciones en la síntesis de valsartan. En una primera variante, el compuesto de fórmula (IIIc), en donde Z3 es formilo, reacciona con una amina primaria de fórmula (IIIa) bajo condiciones de afinación reductiva para proporcionar una amina secundaria, la cual es luego convertida a valsartan. El proceso de afinación reductiva se ilustra bajo condiciones acídicas en los ejemplos 16 y 37. La diferencia técnica entre la preparación de valsartan de acuerdo con la primera variante y la preparación de valsartan de acuerdo con la presente invención es el uso de un proceso de

afinación reductiva bajo **condiciones básicas**, en donde un befinil aldehído sustituido con tetrazol de fórmula (IIa) reacciona con un aminoácido quiral de fórmula (IIb) (en otras palabras, L-valina o un éster de la misma) para proporcionar **sin racemización** una amina secundaria quiral de formula (IIc).

En concordancia, partiendo de la primera variante de D1 el problema técnico subyacente a la presente solicitud es proporcionar un método de reacción de afinación reductiva alternativo y económicamente atractivo para preparar una amina secundaria intermedia quiral para la preparación de valsartan. D1 no menciona ningún proceso de afinación reductiva bajo condiciones básicas. Con los conocimientos de D1 y los problemas de racemización explicados arriba, el técnico con habilidad ordinaria en la materia no podría verse motivado a efectuar una afinación reductiva con un aminoácido quiral en condiciones básicas. Los datos de análisis enantioméricos proporcionados en D1 solo muestran la presencia del enantiómero deseado al final de la reacción, después de la purificación, y en ningún momento permiten deducir que la amina intermedia sea enantioméricamente pura, como la de la presente solicitud antes del proceso de transformación en valsartan.

Cabe anotar que aunque no se muestra que el aminoácido quiral no se racemiza, bajo las condiciones de afinación reductiva en medio ácido, nada puede decirse respecto a la racemización en medio básico, ya que **las rutas mecánicas para la racemización no son las mismas a diferente pH**. Por ejemplo, bajo condiciones ácidas el mecanismo de racemización involucraría enoles y no enolatos. Adicionalmente, las tasas cinéticas para la racemización no serían las mismas a pH ácido que a pH básico. Como se señala en las líneas 7 y 8 de la página 9443 del anexo 2, las tasas de racemización de los aminoácidos dependen del pH y son complejas. Por lo tanto, en vista de D1, el cual se relaciona con la aminación reductiva pero **ilustrada solamente bajo condiciones ácidas**, la elección de llevar a cabo la afinación reductiva en condiciones básicas con un aminoácido quiral no es directa cuando lo que se busca es evitar la racemización durante el proceso de fabricación de una droga como el valsartan. Es así como la falta de racemización, cuando se emplea un aminoácido quiral de fórmula (IIb) en una afinación reductiva bajo condiciones básicas de un bifenil aldehído sustituido con tetrazol de fórmula (IIa), es sorprendente. En consecuencia, la materia objeto de la reivindicación 1 es claramente inventiva por sobre D1.

En una segunda variante, un compuesto de fórmula (IIb), en donde Z3 comprende un hidroxilo esterificado, reacciona con una amina primaria de fórmula (IIa) mediante una reacción de sustitución nucleofílica para proporcionar una amina secundaria de fórmula (IIc), la cual es luego transformada en valsartan. Alternativamente, un compuesto de fórmula (IIIc), en donde Z3 comprende un hidroxilo esterificado, reacciona con una amina primaria de fórmula (IIa)

mediante una reacción de sustitución nucleofílica para proporcionar una amina secundaria de fórmula (IIIb), la cual también puede transformarse en valsartan. La diferencia técnica entre la preparación de valsartan de acuerdo con los dos métodos alternativos de esta segunda variante del proceso de fabricación de valsartan, y la preparación de valsartan de acuerdo con la presente solicitud es el uso de la afinación reductiva en condiciones básicas en donde el bifenil aldehído sustituido con tetrazol de fórmula (IIa) reacciona con un aminoácido quiral de fórmula (IIa) para proporcionar, sin racemización, una amina secundaria de fórmula (IIc).

Consecuentemente, partiendo de la segunda variante de D1, el problema técnico objetivo que subyace a la presente invención es proporcionar un método nuevo y económicamente atractivo para preparar una amina secundaria quiral intermedia para la preparación de valsartan. Aunque D1 contiene enseñanzas relacionadas con la aminación reductiva, como se establece arriba para la primera variante, el técnico con habilidad en la materia no se vería motivado a intentar la aminación reductiva empleando un aminoácido quiral bajo condiciones básicas.

En cuanto a D2, dicha anterioridad divulga un método para la fabricación de antagonistas de angiotensina II de fórmula I, **los cuales no comprende al valsartan**. De acuerdo con D2, una amina secundaria de fórmula 2 (esquema 2a) puede prepararse mediante una reacción de aminación reductiva, en particular como se ilustra en la sección experimental, bajo condiciones ácidas. Como D1, D2 guardan silencio respecto a procesos de aminación reductiva en condiciones básicas llevados a cabo dentro del proceso general y no como un proceso secundario e independiente. Por lo tanto, de la lectura de D2 y conociendo los problemas de racemización (discutidos arriba) y las diferencias entre los mecanismos de racemización para la aminación reductiva bajo pH básico y bajo pH ácido, la persona con habilidad en la materia no habría encontrado en D2 un indicio que lo llevara a realizar una aminación reductiva bajo condiciones básicas con un aminoácido quiral no sería obvio, particularmente en el contexto de la fabricación industrial de una droga comercial como el valsartan, a partir de la combinación de D1 y D2.

En vista de lo anterior, es claro que las reacciones reclamadas en el proceso de la solicitud son novedosas e inventivas por sobre lo establecido en el estado de la técnica citado por el examinador, particularmente considerando que la totalidad del proceso reclamado se lleva a cabo en medio básico, en tanto que en D1 y D2 parte del proceso se desarrolla en medio ácido y otra parte en medio básico.

Por lo tanto, es clara la violación por la **indebida aplicación del artículo 18 de la Decisión 486** en la medida que el arte previo no enseña ni sugiere como llevar a cabo las demás reacciones en un medio ácido y el examinador no proporciona

evidencia alguna que demuestre que dicho conocimiento ya formaba parte de los conocimientos propios del técnico con habilidad ordinaria en la materia.

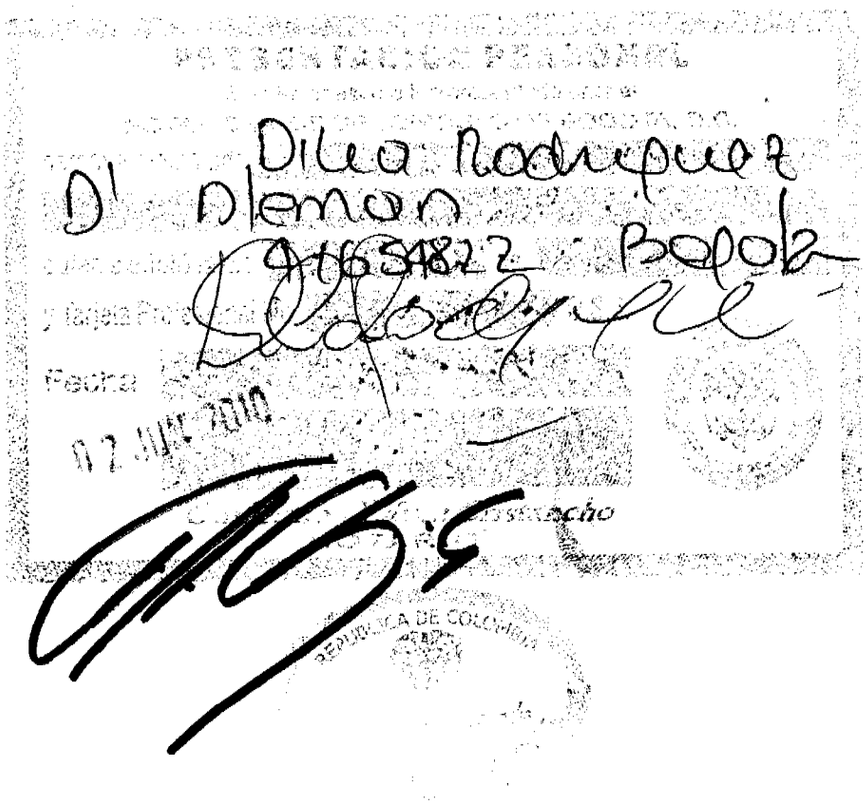
Teniendo en cuenta lo dicho anteriormente, solicito a usted lo siguiente:

a) Que de conformidad con lo previsto por los artículos 3 (inciso 3); 35 (inciso 2) y 59 (inciso 2) del Código Contencioso Administrativo se consideren y se resuelvan TODOS los argumentos y TODAS las cuestiones planteadas así como las que aparezcan con motivo de éste recurso.

b) Que se revoque la resolución No. 23612 de 30 de abril de 2010 expedida por el Superintendente de Industria y Comercio, y se proceda a conceder el privilegio de patente de invención a la solicitud de mi mandante.

Señor Superintendente,

DILIA MARÍA RODRÍGUEZ D´ ALEMAN
C.C. 41.654.882 de Bogotá.
T.P. 20824 CSJ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TETRAHEDRON REPORT NUMBER 423

Controlled Racemization of Optically Active Organic Compounds: Prospects for Asymmetric Transformation

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1. INTRODUCTION

Stereochemistry and chirality are of fundamental importance in modern chemistry[1]. Since the first studies of Pasteur on optical activity there has been a steadily growing interest in the synthesis of optically pure compounds. In the early 1980's an explosive growth in the number of publications on stereospecific and stereoselective reactions took place, probably initiated by the widespread recognition of the importance of using bioactive substances in optically pure form. Racemization, on the contrary, has drawn scarce attention, despite the fact that it often is of essential importance in the industrial synthesis of optically pure compounds[2]. The literature on racemization as the main topic is sparse and mainly focuses on amino-acids and related compounds, and often deals with the avoidance of racemization, *e.g.* in protein synthesis. Racemization procedures are often mentioned only briefly in connection with resolution processes. Moreover, because of the importance of the subject for industry much information is hidden in the patent literature. The aim of this review is to present an overview of available methods and their scope, with the emphasis on information obtained from the patent literature (1967-1996) and to discuss the state of the art of racemization. Racemizations of inorganic and organometallic compounds are not included.

Notwithstanding the revolutionary advances in asymmetric synthesis, the resolution of racemates is still the most important approach in the industrial synthesis of optically pure compounds, as it is often the most economical and convenient way to prepare enantiopure compounds. The main disadvantage of a resolution compared to an enantioselective synthesis is the maximum theoretical yield of 50%. Therefore, racemization of the unwanted isomer is of critical importance for economically- and environmentally acceptable resolutions. In the development of an industrial resolution procedure the racemization of the unwanted enantiomer often presents one of the most difficult obstacles. In many cases rather harsh conditions are necessary, leading to product decomposition, or the substrate has to be modified to make racemization possible. Thus, racemization can easily become an economical bottleneck.

Racemization is defined as the irreversible formation of a racemate from a pure enantiomer and is always associated with the total loss of optical activity. Therefore, compounds which racemize easily are referred to as optically labile. The inversion of one stereocenter in a compound containing several stereocenters is called an epimerization (this leads to change but usually not to complete loss of optical activity if at least one stereocenter in the substrate remains unaffected). Because of this change in optical rotation, epimerization is also referred to as mutarotation, especially in the case of carbohydrates.

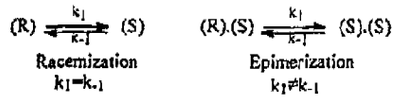


Figure 1. Racemization and epimerization.

A racemate is defined as an equimolar mixture of two enantiomers regardless of their physical state[3]. Crystalline racemates may belong to three different classes: conglomerates, racemic compounds or pseudoracemates[4]. A conglomerate is a mechanical mixture of crystals of the pure enantiomers, whereas a racemic compound consists of equal amounts of two enantiomers embedded in a regular pattern within the

crystal. A pseudoracemate is formed if two enantiomers coexist in an unordered manner in the crystal, thus forming a solid solution. The type of crystalline racemate formed depends not only on the structure of the compound, but also on temperature or pressure. Several examples are known where one form may be converted to another if temperature or pressure are changed.

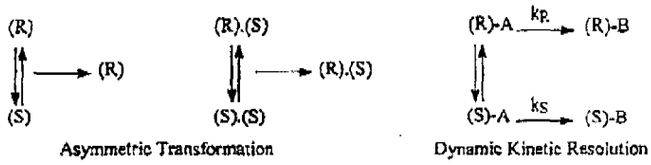


Figure 2. Asymmetric transformation and dynamic kinetic resolution.

In an ideal resolution procedure the racemization should occur simultaneous with the resolution, involving an equilibrium between the two enantiomers from which one of them is removed by an enantioselective process. This is referred to as a crystallization-induced asymmetric transformation if the crystallization of only one of a pair of diastereomers (usually diastereomeric salts) is the enantioselective process[3]. If a chiral compound forms a conglomerate in the solid state and an equilibrium exists between the two enantiomers in a supersaturated solution, crystals of only one isomer can be obtained after seeding the solution with crystals of the desired enantiomer. Finally, if a kinetic resolution is accompanied by an equilibration between the two enantiomers, the process is called a dynamic kinetic resolution[4]. These processes are clearly economically very attractive, but racemization and resolution usually require conditions (*i.e.* temperature, concentration and pH) which are often mutually incompatible. Only by finding the required fine balance between the two, such a process can be achieved. Unfortunately, in most cases the racemization step must be performed separately.

An important part of a racemization procedure is monitoring the progress of the reaction. Especially when the formation of impurities is a problem it is necessary to stop the process at a well chosen moment. In most cases following the loss of optical rotation will be adequate. This method has the advantage that it can be used to follow the progress of the reaction continuously. However, when the optical rotation is too low, when impurities interfere or when the solution strongly absorbs light, alternative methods have to be applied, *i.e.*, spectroscopic methods, such as NMR, or chromatographic techniques[7].

2. KINETICS OF RACEMIZATION

The driving force of the racemization process can be predominantly attributed to the increase of entropy caused by the mixing of the two enantiomers. Although differences in interaction between enantiomers (R-R, or S-S vs. R-S interactions) can lead to a non-zero enthalpy contribution, this may usually be ignored, thus $\Delta G^\circ \approx RT \ln \frac{1}{2}$. This corresponds to -0.41 kcal/mol (-1.7 kJ/mol) at 25°C.

Two different definitions for the rate of racemization have been reported[8]. The rate of racemization can be described either as the rate of interconversion of enantiomers, or as the rate of formation of the racemate. The interconversion of enantiomers can be described by reversible first-order kinetics[9] (equation 1)

$$(R) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (S)$$

$$-\frac{d[R]}{dt} = k_1[R] - k_{-1}[S] \qquad (1)$$

where [S] and [R] are the concentrations of the enantiomers S and R, k_1 and k_{-1} are the interconversion constants for the R and S enantiomer respectively, and t is the time. Initially, when one of the enantiomers dominates, there is a chiral medium present and $k_1 \neq k_{-1}$. In the solid state this difference may be substantial, however, in a solution the difference will be negligible and it may be assumed that $k_1 = k_{-1} = k$. If the racemization starts from a pure enantiomer R, the elaboration of this first-order differential, with the conditions $[R]_0 - [R]_t = [S]_t$ is:

$$\ln\left[\frac{[R]_0}{2[R]_t - [R]_0}\right] = 2kt \qquad (2)$$

where $[R]_0$ is the concentration of enantiomer R at time zero and $[R]_t$ at time t.

Racemization can also be described as the forming of a racemate from a pure enantiomer in an irreversible first-order reaction[9] (equation 3)

$$2\,(R) \xrightarrow{k'} (RS)$$

$$-\frac{d[R]}{dt} = k'[R] \qquad (3)$$

With the condition $[R]_0 - [R]_t = 2[RS]_t$ this equation can be transformed to

$$\ln\left[\frac{[R]_0}{[R]_0 - 2[RS]_t}\right] = k't \qquad (4)$$

where $[RS]_t$ is the concentration of racemate at time t and k' is the racemization constant. When the racemization process is followed by the loss of optical activity, equation 4 can be transformed to:

$$\ln\left[\frac{\alpha_0}{\alpha_t}\right] = k't \qquad (5)$$

where α_0 is the optical rotation at time zero and α_t at time t.

It should be noted that $k' = 2k$, implying that the rate of racemization equals to twice the rate of interconversion of enantiomers.

Another frequently used variable to describe racemization or epimerization is the racemization half-life $t_{1/2}$ (also denoted as τ) which is the time required to obtain a mixture with an enantiomeric excess of 50%. Calculated from equation 2 this results in:

$$t_{1/2} = \frac{\ln 2}{2k} \qquad (6)$$

and from equation 4 in

$$t_{1/2} = \frac{\ln 2}{k'} \qquad (7)$$

3. STATISTICAL OVERVIEW OF RACEMIZATION METHODS

Considering the literature in the period 1967-1996, nine methods of racemization can be distinguished, and the substrates used in these racemizations can be classified into nine classes of compounds. Counting the number of papers on the respective methods, as applied to the selected classes of compounds provides a useful overview of the scope and limitations of racemization techniques. This is summarized in table 1. Several conclusions from this classification can be drawn:

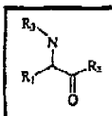
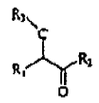
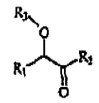
Based on *classes of compounds*:

- α-Amino-carboxylic acids and derivatives: Almost half of the total number of papers deal with amino acids or derivatives, demonstrating the industrial importance of these compounds. Base and enzyme catalyzed racemizations and racemizations with a Schiff base intermediate are of equal importance and are responsible for 80% of the cases. Acid catalyzed and thermal racemization are of lesser interest.
- α-Alkyl-carboxylic acids and derivatives: About 17% of the reports deals with racemization of α-alkyl-carboxylic derivatives. These references pertain mainly to profens and chrysanthemic acids (both industrially important compounds) which are usually racemized by base- (52%) or acid- (24%) catalysis. Some examples using thermal or enzymatic racemization are reported.
- α-Oxy-carboxylic acids and derivatives: Approximately 11% of the studied literature refers to α-hydroxy- and α-alkoxy-carboxylic acids or derivatives, mostly involving base-catalyzed racemization (60%). Enzyme-catalyzed racemization (21%) is also of some importance and can be attributed exclusively to the use of mandelic acid racemase.
- α-Substituted nitriles: Racemization of chiral nitriles is of minor importance. Substrates bearing an α-hydrogen are usually racemized by base. In the absence of an α-hydrogen, racemization is possible by nucleophilic substitution with cyanide.
- Amines: Racemization of chiral amines is generally performed by oxidation-reduction (60%), or by base-catalysis (30%).
- Alcohols and Oxy-compounds. Only 2% of the references are referring to chiral alcohols, alkoxides, acetates and ethers. Thermal, base-catalyzed and enzyme-catalyzed racemization have been reported.
- Halides: Like alcohols, only a few examples are known for racemization of chiral halides (2%). Racemization via addition-elimination or substitution seems to be the best procedure, followed by base-catalysis. More reports on racemization of halides are encountered in the literature covering dynamic kinetic resolutions, *e.g.* about base-catalyzed racemization of α-halocarboxylic derivatives.
- Rotamers: Racemization of rotamers (usually biaryls) is performed thermally and is in some cases catalyzed by additives.

Based on *racemization methods*:

- Base-catalyzed racemization: Almost one third of the reports deals with base-catalyzed racemizations. It is by far the most important method currently used for racemization of optically pure organic compounds, its scope is large and it can be applied to almost all compounds bearing an acidic hydrogen at the chiral center.

Table 1. Classification Matrix of Racemization by Methods and Classes of Compounds[a].

Compound \ Racemization Method	Thermal	Base-catalyzed	Acid-catalyzed	Schiff base intermediate	Enzyme-catalyzed	Redox	Nucleophilic substitution	Meso-intermediate	Photo-chemical	Total
	15	57	25	66	56	4	0	1	0	224 (45.5%)
	8	43	20	0	4	1	0	3	4	83 (16.9%)
	2	31	4	0	11	2	0	2	0	52 (10.6%)
	0	9	0	0	1	0	7	0	0	17 (3.4%)
	4	13	1	0	0	27	0	1	0	46 (9.3%)
	3	4	5	0	2	0	0	1	0	15 (3.0%)
	1	2	4	0	0	0	5	0	0	12 (2.4%)
Rotamers	29	0	0	0	0	0	0	0	0	29 (5.9%)
Miscellaneous	9	2	3	0	0	0	0	0	0	14 (2.8%)
Total	71 (14.4%)	161 (32.7%)	62 (12.6)	66 (13.4%)	74 (15.0%)	34 (6.9%)	12 (2.4%)	8 (1.6%)	4 (0.8%)	492

a) The numbers in this matrix refer to the number of reports on the indicated item in the period 1967-1996.

- Schiff-base mediated racemization: Racemization via Schiff bases are only feasible for compounds bearing a free primary amino group at the chiral center. Nevertheless, this racemization procedure is very

extensively studied and is important in industry because of its application to the racemization of amino acids.

- Enzyme-catalyzed racemization: Of the total number of references, 15% deal with enzyme-catalyzed racemization. The scope of racemization by racemases is still limited, and mainly restricted to amino acids and derivatives (75%) and to α-hydroxy-carboxylic acids and derivatives (15%). Efforts are reported to apply enzyme-catalyzed racemization to other classes of compounds.
- Thermal racemization: The scope of thermal racemization (14%) is wide and it is an industrially attractive method because it is simple and cheap. The main problem with this method is usually decomposition of the substrate when high temperatures have to be applied. Good substrates for thermal racemization are compounds which racemize by rotation or deformation of bonds (biaryls), by pyramidal inversion or by rearrangement of bonds; these account for more than 50% of the examples of thermal racemization.
- Acid-catalyzed racemization: The scope of acid-catalyzed racemizations is more limited than that for base-catalyzed reactions and is usually restricted to compounds capable of some form of keto-enol tautomerism. α-Substituted carboxylic acids and derivatives account for 87% of the substrates used.
- Oxidation-reduction: Only 8% of the total number of references deals with racemization by redox reactions. Of these, 80% refers to racemization of chiral amines. Some racemization procedures are rather complex (multistep), and therefore industrially not attractive. Chiral alcohols also appear to be good substrates for this racemization approach.
- Nucleophilic substitution: Racemization of chiral substrates by nucleophilic substitution or addition-elimination sequences (3% of the total) is restricted to chiral halides and nitriles. This method, requires that the substituent at the chiral center is a good leaving group as well as a good nucleophile. An advantage of this method is that it can be used for compounds without a hydrogen at the stereocenter.
- Racemization via an intermediate meso-compound: Racemization in which the asymmetric center itself is not involved is possible by making two of the functionalities attached to the stereocenter equal, resulting in an achiral meso-compound. A few examples (2% of the total) of this method are known and mainly involve di-carboxylic acid derivatives or di-acetates. This method can be applied to compounds without a hydrogen at the chiral center.
- Photochemical racemization: Racemization by photochemical reactions appears to be a method of little value. Only a few examples are known (1%) and are all related to cyclopropane derivatives (chrysanthemic derivatives).

4. RACEMIZATION METHODS

To convert an enantiomerically enriched mixture into a racemic mixture two approaches are available, the simplest being the addition of the other enantiomer. Obviously this will be used only under special circumstances, such as during the measurement of phase-diagrams or in the development of methods for the determination of an enantiomeric excess. Otherwise it is necessary to invert an enantiomer into its mirror image by physical or chemical methods. The classification matrix presented (Table 1) will be used for a detailed treatment of the various methods of racemization.

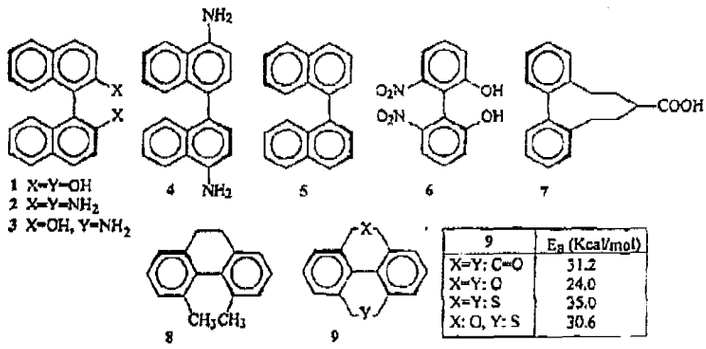
4.1 Thermal racemization

Many optically active compounds can be racemized by simply heating them to an appropriate temperature without any additional reagent. The main requirement for the success of this method is that the substrate must have a sufficient thermal stability under the conditions used. Therefore, the scope of this method is limited. Slow racemization at temperatures close to or below room temperature is often referred to as spontaneous racemization.

Thermal racemization can occur by various mechanisms. Several compounds without a specific chiral center racemize by rotation about a bond. Other mechanisms involving no bond breaking are the simultaneous deformation of several bonds and the inversion of hetero-atom chiral centers. At higher energy levels pathways involving the breaking or rearrangement of bonds such as tautomerism, retro-Diels-Alder/Diels-Alder, and radical processes can occur. For acids and bases thermal racemization may take place but, depending on the compound, this may also be considered as an (auto-)catalytic process.

4.1.1 Racemization by rotation about a single bond

Compounds whose chirality depends on the hindered rotation about a single bond can very often be racemized by heating to a sufficiently high temperature. This behavior is frequently observed for substituted binaphthyls. Racemization of binaphthyls 1-3 is spontaneous. A crystallization-induced asymmetric transformation is observed by diastereomeric complexation with $CuCl_2$-sparteine or $CuCl_2$-α-methylbenzylamine[10]. 1,1'-Bi-2-naphthol 1 can also be racemized in the melt which likewise can be extended to a crystallization-induced asymmetric transformation by complexation with chiral diamines[11].



9	E_a (Kcal/mol)
X=Y: C=O	31.2
X=Y: O	24.0
X=Y: S	35.0
X: O, Y: S	30.6

Figure 3. Thermally racemizable biaryls.

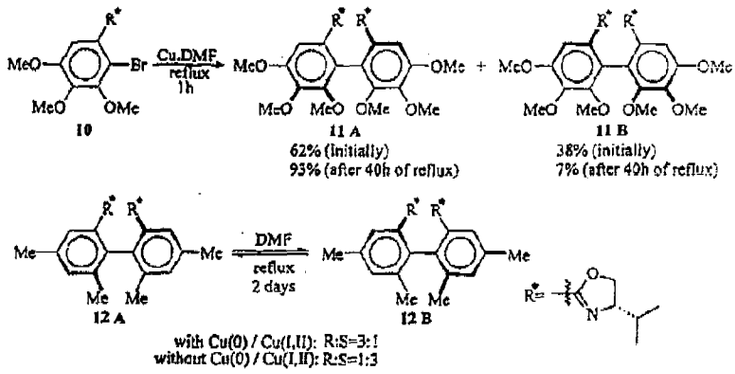
Racemization in the solid state at 150°C is observed for binaphthyls 4 and 5. These compounds form polymorphic crystals, and racemate and conglomerate can coexist in a wide range of temperature. Derivative 4 forms a stable racemate between room temperature and 197°C, and a conglomerate in the range 197-204°C. In this case a crystallization-induced asymmetric transformation can be performed at 204°C by a solid-melt-solid conversion, or by a solid-solid conversion at 197°C[12]. For 1,1'-binaphthyl 5 the temperature ranges are room temperature to 145°C (racemate) and 145-158°C (conglomerate)[13]. 1,1'-Binaphthyl 5 can also be

racemized in solution[14] which can be catalyzed homogeneously by formation of a radical anion[15] or heterogeneously by activated carbon, modified carbon catalyst, electron-donor surfaces[15] or platinum[14].

A study of the solvent effect on the racemization of biphenyl derivative 6 showed that the inversion rate of the dianion was accelerated going from a water to a DMSO solution. This was explained by desolvatation of the dianion in DMSO[16].

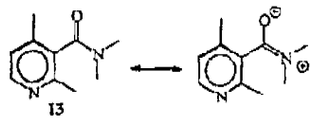
The bridged biphenylcarboxylic acid 7 racemizes in *o*-xylene at 50°C ($t_{1/2}$=53 min.). A crystallization-induced asymmetric transformation of 7 was observed via diastereomeric salt formation with quinidine[17]. The racemization of bridged biphenyls 8 and 9 have been studied. The experimental activation energies were in good agreement with those calculated by MM methods[18].

A first-order asymmetric transformation was observed during the asymmetric Ullmann reaction to non-racemic biaryls 11 and 12 (Scheme 1). Initially, in the Ullmann reaction of 10 to biaryl 11 a A/B ratio of 62/38 was observed, which under thermodynamic equilibrating conditions in solution changed to A/B=93/7. Refluxing a mixture of 12A and B in DMF with Cu(0)/Cu(I,II) for two days resulted in a A/B ratio of 3/1 while refluxing in DMF without a catalyst resulted in a A/B ratio of 1/3[19].



Scheme 1. First-order asymmetric transformation of biaryls.

The chirality of nicotinamide analogue 13 is also the result of hindered rotation (atropisomerism). Thermal racemization of 13 is solvent dependent and the highest inversion rate is obtained by performing the reaction in an apolar solvent such as hexane. This is explained by assuming that rotation about the Ar-C(O) bond is coupled with rotation about the C(O)-NMe_2 bond (scheme 2). An apolar solvent will decrease the double bond character of the C(O)-NMe_2 bond and facilitate this coupled rotation[20].



13

Scheme 2.

4.1.2 Racemization by simultaneous deformation of several bonds.

Sometimes racemization is only possible by simultaneous rotation and stretching of several bonds. Typical examples are the helicenes which can undergo thermal racemization, because apparently the helical configuration is more flexible than expected. [9]-Helicene, for example, racemizes in 10 min. at 380°C ($\Delta G^{\ddagger}$=43.5 kcal/mol)[21] and [11]-helicene at 400-410°C[22]. It has been demonstrated by isotopic labeling that the racemization is not the result of a double internal Diels-Alder, but is most likely to occur through bending and stretching of bonds without breaking them. Heterohelicenes show a similar behavior[23].

Other examples are the 'crown-to-crown' interconversion of cyclotriveratrilene **14** at room temperature ($\Delta G^{\ddagger}$=26.5 kcal/mol)[24] and the thermal ring inversion of chiral substituted cyclooctatetraenes such as **15**[25].

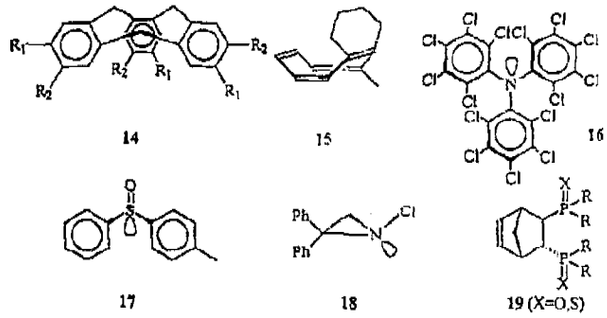


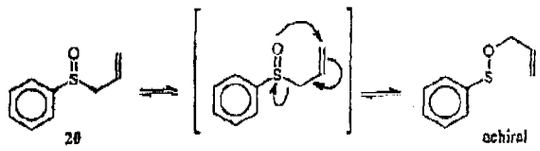
Figure 4. Thermally racemizable compounds.

4.1.3 Racemization by pyramidal inversion of a heteroatom chiral center.

Compounds with a chiral center at a heteroatom bearing three substituents and a lone pair of electrons (*i.e.* amines and sulfoxides) can racemize or epimerize by a pyramidal inversion of this center. Perchlorotriphenylamine **16**, a propeller-shaped chiral compound, racemizes at 120°C ($\Delta G^{\ddagger}$=31.4 kcal/mol), but this racemization does not occur by a nitrogen inversion but is assumed to proceed by a 'two-ring flip' mechanism[26]. Examples of pyramidal inversions are the racemizations of compounds **17** and **18**. Chiral sulfoxide **17** racemizes at 200°C in xylene ($\Delta G^{\ddagger}$=38.6 kcal/mol)[27] and chiral aziridine **18** in carbon tetrachloride ($\Delta G^{\ddagger}$=24.4 kcal/mol)[28].

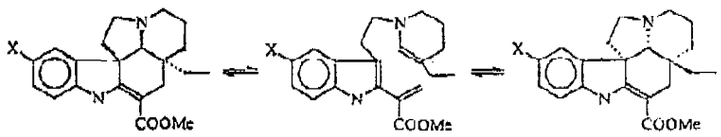
4.1.4 Racemization by a rearrangement.

It may be suggested that allyl *p*-tolylsulfoxide **20** racemizes by inversion of the chiral heteroatom ($\Delta G^{\ddagger}$=24.7 kcal/mol at 51°C in benzene). However, a study of the racemization mechanism using isotope labeling revealed a reversible [2,3]-sigmatropic rearrangement which proceeds via a lower energy reaction path (scheme 3)[29]. The optical stability of chiral sulfoxides has been reviewed by Solladie[30].



Scheme 3. Racemization of allyl *p*-tolylsulfoxide.

Unlike the previous examples where no bonds were broken this is the first example of a thermal racemization which occurs through the reorganization of bonds. Several types of rearrangement may lead to racemization, *e.g.* the alkaloid vincadifformine **21a**, which is racemized in 20 min. by microwave irradiation in DMF[31], and the racemization of its derivative **21b** by refluxing in dichlorobenzene for 14h in a yield of 78%[32]. A successive retro-Diels-Alder/Diels-Alder reaction is responsible for this remarkable simultaneous inversion of three chiral centers (scheme 4).

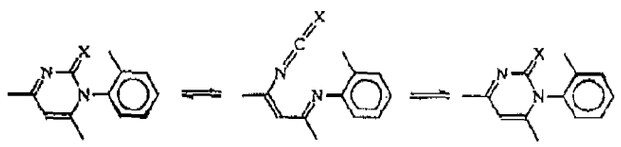


21a (X=H)
21b (X=Br)

Scheme 4. Racemization of vincadiffomine.

The racemization of optically active tertiary phosphine oxides or sulfides **19** (especially R=Ph, "NORPHOS") also proceeds via a (retro)-Diels-Alder reaction in the presence of (di)-cyclo-penta-1,3-diene at 160°C in yields exceeding 90%[33].

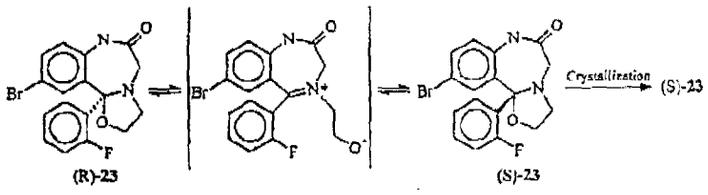
A comparable mechanism is suggested for the racemization of heterobiaryls **22**. In contrast to other biaryls this mechanism does not proceed by rotation about the N-Ph bond but by reversible ring opening and closure (scheme 5)[34].



22 X=O,S

Scheme 5. Racemization of heterobiaryls.

It has been suggested that racemization of oxazolebenzodiazepinone **23** occurs via ring opening to an achiral quaternary iminium salt intermediate (scheme 6). After seeding a supersaturated methanolic solution of racemic **23** with one of its pure enantiomers at room temperature, a crystallization-induced asymmetric transformation is observed and optically pure (S)-**23** is isolated in a yield exceeding 70%[35].



Scheme 6. Racemization and asymmetric transformation of oxazolebenzodiazepinone.

Other examples of racemizations involving ring opening reactions and/or rearrangement of bonds are given in figure 5. Racemization of furanones **24** can be performed by heating under neutral conditions which is probably the result of a ring opening and subsequent ring closure of the cyclic ketal. Racemization of **24b** can also be performed under weakly acidic conditions which probably involves a furan derivative. A dynamic kinetic resolution of 5-hydroxy-2(5H)-furanones **24a** was obtained conducting a lipase catalyzed acetylation in quantitative yield and ee's up to 100%[36]. In the case of 5(R)-menthyloxy-2(5H)-furanone **24b** epimerization leads to a crystallization-induced asymmetric transformation with a yield of 80% of one diastereomer[37].

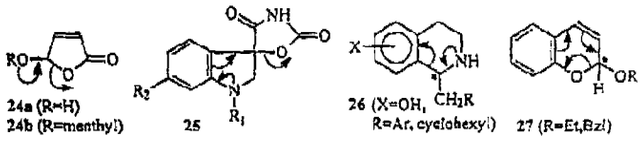
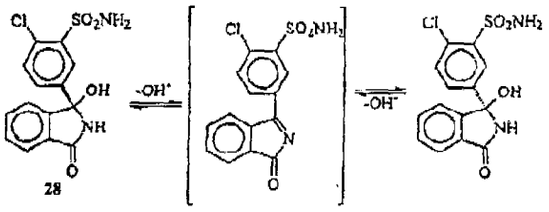


Figure 5.

Spiro-oxindoles **25** are racemized by heating in DMF at 80-200°C for at least 24 h[38] and tetrahydroisoquinoline derivatives **26** by heating at 180°C for 5 min in vacuo[39]. Racemization of chiral chromenes **27** follows a first-order reaction at temperatures between 70 and 85°C in different solvents. A persuasive mechanism involving a dienone intermediate is postulated[40].

Racemization is also possible by elimination of a substituent from a chiral center followed by reattachment. This is the case with chlortalidone **28** which is racemized in aqueous media at room temperature via elimination-addition of hydroxide ($\Delta G^{\ddagger}$=21.6 kcal/mol). A study of the kinetic and activation parameters of the reaction revealed dynamic equilibria via a carbonium and ammonium intermediate (scheme 7)[41].



Scheme 7. Racemization of chlortalidone.

Another example is the racemization of 1,2-dihalogeno-cyclopentanes or cyclohexanes **29** in a trans or threo configuration which shows first-order kinetics. It is proposed that this is the result of a diaxial-diequatorial rearrangement involving a halonium intermediate (scheme 8)[42].

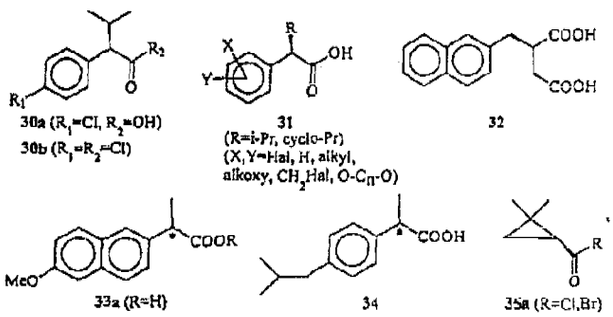
29 X,Y=Cl,Br; n=1,2

Scheme 8.

4.1.5 Racemization involving a tautomeric equilibrium.

Compounds bearing a keto function in an α-position to a chiral center can racemize through a keto-enol equilibrium. Thermal racemization of α-alkyl substituted carboxylic derivatives which follow this mechanism are summarized in Table 2. The important pharmaceuticals naproxen and ibuprofen can be racemized thermally. Naproxen **33a** is racemized in t-BuOH at 140°C[46] and ibuprofen **34** is racemized at 220°C[47]. The cyclopropanecarboxylic acid chloride and bromide **35a** are racemized thermally at 100-200°C. This racemization does not occur via ring opening but via enolization or ketene formation.

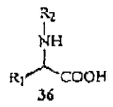
Table 2. Thermal Racemization of α-Alkyl Substituted Carboxyl Derivatives.



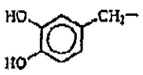
Entry	Compound	Racemization conditions	Yield (%)[a]	Ref
1	**30a**	inert solvents (hydrocarbons), T>150°C, N_2, 3-12 h	n.r.	43
2	**30b**	inert solvents (hydrocarbons), T>150°C, N_2, 3-12 h	n.r.	43
3	**31**	liquid or vapor phase, T=200-350°C, inert atmosphere.	n.r.	44
4	**32**	200°C, 1 hour	99	45
5	**33a**	t-BuOH, autoclave, 140°C, 22 h	n.r.	46
6	**34**	heating in the melt, 220°C	n.r.	47
7	**35a**	100-200°C during 12 h under N_2 in hydrocarbon or ether	n.r.	48

a) n.r. = not reported.

Table 3. Thermal Racemization of Amino Acid Derivatives



36

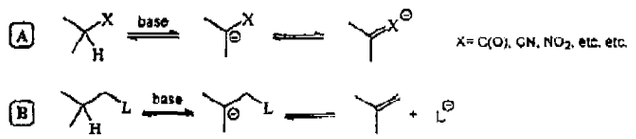
Entry	R_1	R_2	Racemization conditions	Yield (%)[a]	Ref
1	$H_2N(CH_2)_4$-	H	H_2O, Glycol, 120°C, 24 h	95	49
			145°C, 24 h	75	50
			H_2O, 170-200°C, 30 min	n.r.	51
2		H	H_2O, 175°C, 2 h	n.r.	52
3	Ph	H	H_2O, 160°C, 6 h	65	53
4	$HOCH_2$	H	H_2O, <150°C, 5 h, autoclave	84	54
			H_2O, 200°C, 60 kg/cm^3, 1 h	90	55
5	Ph	CH_3CO	H_2O, 150°C, 6 h	94	56
6	Bzl	CH_3CO	hydrocarbon, >130°C, few h	n.r.	57
7	all amino acids	CH_3CO	melt, 100-200°C, N_2, 30 min	100	58
8	-CH_2-CH_2-CH_2-CO-		melt, 205-250°C, N_2, 4 min	n.r.	59

a) n.r. = not reported.

The industrially important thermal racemizations of amino acids and their derivatives without any catalyst are known to proceed with relative difficulty, especially in aqueous solutions. These racemizations are performed at high temperatures and often under pressure. The attractiveness of such methods is that they are relatively cheap and therefore industrially attractive. The critical feature of thermally racemizing amino acids and derivatives (**31**) is its performance with a minimum amount of product decomposition. Thermal racemizations of amino acids and derivatives are summarized in table 3.

4.2 Base-catalyzed racemization.

Base-catalyzed racemization is a well-known, and probably the most frequently used, method for racemization or epimerization of optically pure compounds. It usually involves the removal of a hydrogen from the chiral center to form a carbanion. This carbanion must be stabilized by adjacent groups such as keto, nitrile, nitro or other functionalities (scheme 9.A), or by a reversible elimination of a β-substituent (scheme 9.B).



Scheme 9. Mechanisms for base catalyzed racemization.

Base-catalyzed racemizations often require the preparation of a derivative with an enhanced acidity. From an industrial point of view this is undesirable as it introduces additional reaction steps unless the derivatization is reversible and can be performed in situ. In general, optically active substrates can undergo

either racemization, retention or inversion in base-catalyzed reactions. Whether readdition of the removed hydrogen occurs predominantly at the same side as from which it was removed (retention), predominantly from the opposite site (inversion) or at random (racemization) depends on several parameters like solvent, substituents and character of the base.

In apolar solvents removal of a hydrogen by a base results in an intimate ion pair and readdition of the proton may lead to some preference for retention and therefore to a relatively slow racemization. In a protic solvent a solvent separated ion pair is generated. Readdition occurs predominantly from the opposite side resulting in a net inversion and fast racemization[60]. In aprotic polar solvents anions are less solvated than neutral species or cations. Therefore bases tend to be more reactive in these solvents than in protic solvents. Amino acid derivative **37a** for instance shows an isotope exchange which is equal to the rate of racemization (tBuOK/tBuOH, $k_e/k_a=1$; k_e is the isotope-exchange constant and k_a the racemization constant). However, a net initial retention was observed for derivative **37b** ($k_e/k_a=2.4$) which is assumed to be the result of a combination of sterical effects and complexation with potassium ion[61].

The influence of substituents is demonstrated in the racemization of chiral ketones **38**. Whereas ketone **38a** racemizes with a half-life $t_{1/2}$ of 18.4 min., ketone **38b** racemizes with $t_{1/2}$=13.7 min., both with NaOEt as base in EtOH at 25°C[62].

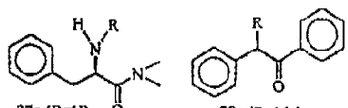
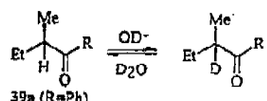


Figure 6.

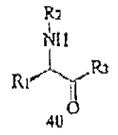
In a kinetic isotope study of the racemization of optically active phenone **39a**, it was found that the racemization proceeds with a rate equal to the rate of enolization following a S_E1 mechanism[63]. The kinetics of the base catalyzed racemizations of chiral ketones **39b** have been studied at different basicities[64].

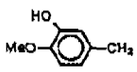
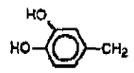
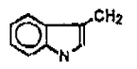
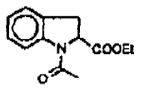
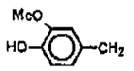
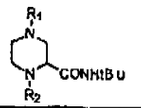


Scheme 10.

Bases generally used for racemization include hydroxide, metal alcoholates, metal amides and amines. The fluoride ion can also be used as a base, as was shown in the racemization of phenylalanine derivatives. Treatment with $nBu_4N^+F^-$ in THF at ambient temperature for two hours leads to racemization[65].

Table 4. Base-catalyzed Racemization of Amino Acids and Derivatives.

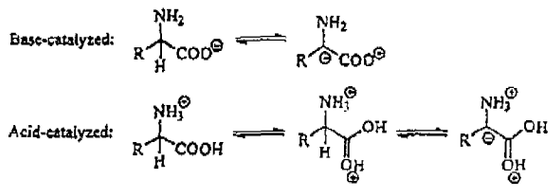


Entry	R_1	R_2	R_3	Conditions	Yield (%)[a]	Ref
1	all amino acids	H	OH	NaOH, H_2O, pH>10, LiCl, T=100-250°C	n.r.	66
2	CH_2OH	H	OH	NH_4OH, RNH_2, pH=5-8, 105-116°C	>90	67
3	Ph	H	OH	NaOH, pH=11-13, 100-120°C, 1.5-4 h	n.r.	68
4		H	OH	NaOH, KOH, H_2O, 40-100°C	93	69
5		H	OH	NH_3, RNH_2, pyridine, basic ion exchange resin, MeOH, 45°C, 30 min	64	70
6	$-(CH_2)_2-COOH$	H	OH	42% NaOH, 160°C, 3 h	93	71
7	$-(CH_2)_2-NH_2$	H	OH	$(NH_4)_2SO_4$, H_2O, 150-250°C, 2 h	100	72
8	all amino acids	H	OR	RO^- in R'COOR, 0-40°C	n.r.	73
9	$CH(CH_3)_2$	H	OR	NaOMe, 25°C, 20 min	93	74
10	RR'C=N-OCH_2-	H	OR"	NaOEt, EtOH	n.r.	75
11	all amino acids	H	NR_2	NaOH, NaOR, NR_3, 80-110°C, organic solvent + 5 vol. % H_2O	n.r.	76
12	$-(CH_2)_4-NH_2$	H	NH_2	NaOH, NH_4OH, $NaNH_2$ in NH_3, 100°C, 8 h	n.r.	77
13	Bzl	H	NH_2	NH_3, ROH, MCl_n, autoclave, 100°C	94	78
14	all amino acids	CH_3CO	OH	NR_3, DMSO or DMF, HOBt, 100°C	n.r.	79
15		CH_3CO	OH	NaOH, H_2O, pH=9, 70°C	94	80
16	Ph	CH_3CO	OH	2N NaOH, 70°C	75	81
17	$-(CH_2)_2-S-CH_3$	CH_3CO	NH_2	NaOH, KOH, LiOH, ROH	85	82
18				NaH, DMF, 22°C, 15 min	92	83
19		PhCO	OMe	Na_2CO_3, DMF, 120-130°C, 2 h	n.r.	84
20	Bzl	RCH_2CO	OR'	DBU, DBN, TMG, pH>12, RT	n.r.	85
21	Ph	COOEt	OH	NaOH, 40°C, 5 h	95	86
22	Ph	COOMe	OH	NaOH, NH_4OAc, MeOH-H_2O, 60-150°C, 8 h	92-99	87
23				NH_3, NH_2R, MeOH, H_2O, 150-160°C, 8-15 h	50-90	88
24				KOtBu, cyclohexane and THF, RT-250°C, 7 h	n.r.	89

a) n.r. = not reported.

4.2.1 Racemization of amino acids and related compounds.

A generally accepted mechanism for the acid and base-catalyzed racemization of amino acids is outlined in scheme 11[70]. The racemization is consistent with a S_E1 mechanism and shows a Hammet relation with β=1.15 for arylglycines at pH=10. A pH profile study showed general base catalysis and first-order kinetics[91]. The base-catalyzed racemizations of amino acids and their derivatives are tabulated in Table 4. They can be subdivided into three main classes based on the applied bases: metal hydroxides, metal alkoxides or carboxylates and amines.



Scheme 11. Acid and base-catalyzed racemization of amino acids.

Free amino acids are usually racemized by hydroxides, amino acid esters by the corresponding alkoxides, amino acid amides by the corresponding amines or hydroxides and N-acyl or N-carbonyloxyalkyl amino acids by amines or hydroxides. The yields of base-catalyzed racemizations of amino acid derivatives are usually good. Factors influencing the acidity of the α-hydrogen of amino acids, and thus the rate of racemization, are the electronegativity of the substituent R_1, decrease of the negative charge of the carboxylate and substitution at the carboxylic and amino site[92]. The use of a simplex optimization algorithm for the determination of absolute racemization constants of amino acids gave results consistent with the proposed mechanism and factors influencing the racemization rate[93].

It should be mentioned that a substantial fraction of the literature on racemization of amino acid derivatives is published in patents dealing mainly with the resolution of amino acid derivatives. These patents, in which the racemization step is described in detail neither in the body of the patent nor in examples, have not been included in this review.

4.2.2 Asymmetric transformations of amino acids and related compounds.

If the substrate in a classical resolution of an amino acid or amino acid derivative has a sufficiently high acidity or if the resolving base is a sufficiently strong base, an in situ racemization leading to an asymmetric transformation becomes possible.

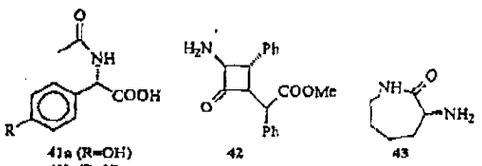
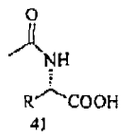


Figure 7. Base-catalyzed asymmetric transformation of amino acid derivatives.

A crystallization-induced asymmetric transformation has been observed for N-acetyl-(*p*-hydroxyphenyl)glycine **41a** by the action of excess optically active resolution base α-methylbenzylamine (MBA) in a hexanol/cumene solution at 130°C. Optically pure amino acid derivative **41a** was isolated in 90% yield and the in situ racemization was initiated by the excess MBA. A study of the racemization rate of N-acetyl-amino acids **41** showed an inductive effect of the side chain of amino acids following a Hammet-relation (Table 5)[54]. A crystallization-induced asymmetric transformation of **41a** was also observed with 2-4 eq. (R)-2-amino-1-butanol in butanol/toluene with 87% yield and 85% ee[91] and for phenylglycine **41b** with 2 eq. (R)-MBA in butanol/xylene with 95% yield and 100% ee[54].

Table 5. Racemization rate (k_{rac}) of N-acetyl amino acids[a]

R	k_{rac} (s^{-1})
Me	0.04
p-OH-Bzl	0.23
Bzl	0.32
p-OH-Phe	3.17
Phe	8.38

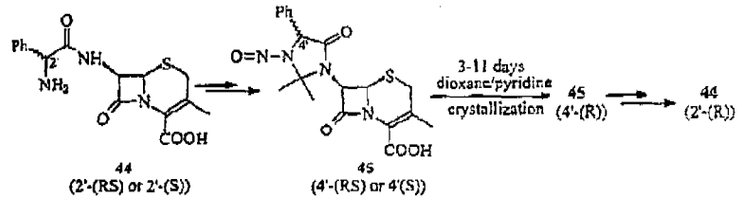


41

a) 1 eq. **41**, 5 eq. (RS)-MBA, hexanol, 130°C

A crystallization-induced asymmetric transformation of **42** was encountered in the asymmetric synthesis of β-lactams; the in situ epimerization under crystallization conditions was performed at -30°C by Et_3N in Et_2O[97]. α-Aminocaprolactam (ACL) **43**, a precursor for lysine, is racemized by strong base (NaOH, NH_4OH or $NaNH_2$) in anhydrous NH_3 at 100°C during 8 h[98], by sec-$BuNH_2$ or Et_3N at 130°C during 6 h[99] or by $NiCl_2$ in alcohol solutions at 95°C during 4 h[100]. An asymmetric transformation of ACL **43** can be achieved by forming a diastereomeric complex with $NiCl_2$. The reaction is carried out by reacting racemic **43** with anhydrous $NiCl_2$ in an alcohol solution and the supersaturated solution is then seeded with optically pure $(l\text{-ACL})_3NiCl_2.EtOH$ at temperatures ranging from room temperature to 120°C. In situ epimerization was initiated by a basic catalyst ($Ni(OH)_2$ or $Ni(OR)_2$) and optically pure ACL **43** was isolated in yields up to 86%[101].

A crystallization-induced asymmetric transformation of β-lactam derivative **45** is attained in the asymmetric synthesis of cephalexin **44**. In situ epimerization of N-nitrosoimidazolidinyl derivative **45** is achieved by base under slow crystallization and yields optically pure **45** in 76%, which subsequently has been converted to enantiopure **44** (scheme 12)[102].



Scheme 12. Asymmetric synthesis of cephalexin.

An unusual racemization was observed for N-phthalyl-α-amino acid chloride **46** (figure 8). It is proposed that racemization by tertiary amines occurs via a ketene intermediate. Racemization via this method was also observed for (O-acetyl)mandelic acid[103]. The ketene intermediates obtained from α-aryl-acetic acid chlorides could be trapped with optically pure pyrrolidinone **47**, resulting in a stereoselective esterification giving optically pure α-aryl-acetic acid esters in high yield and large diastereomeric excess[104]. Some amino acid derivatives can be racemized under very mild conditions. Racemization of propiophenone **48** for example was achieved by reaction with $NaHCO_3$ in CH_2Cl_2 at 40°C for 1-2 h[102].5-Substituted hydantoins **49** are easily racemized under weakly basic conditions (pH=7-9) at relative low temperatures (30-40°C). Yields are quantitative and the racemization can be performed in aqueous solutions using phosphate buffer, NaOH[106] or basic ion exchange resin[107].

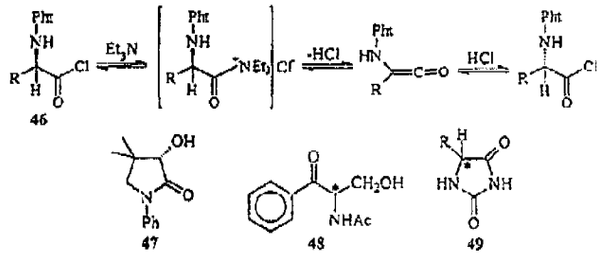
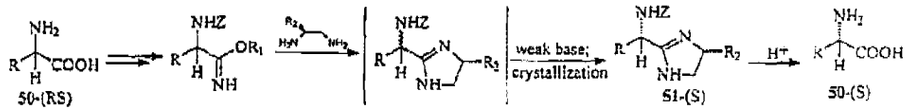


Figure 8. Optically labile amino acid derivatives.

In general, racemization of hydantoins is mainly dependent on substitution at the 5-position, polarization of the proton at the 5-position and activation by substituents[108-109]. The simple synthesis of optically labile hydantoins from optically stable amino acids is a common method to promote racemization at the α-position[110]. Another method to promote the acidity of the α-proton in amino acids **50** is by conversion into imidazolidines **51** via an iminoether coupling with a diamine (scheme 13). These optically labile compounds can undergo a crystallization-induced asymmetric transformation under weakly basic conditions, and the first-order epimerization is catalyzed by amines. Starting from alanine (R=Me) and under influence of optically pure (S)-2-(aminomethyl)pyrrolidine, optically pure alanine is isolated in yields exceeding 50%[111].



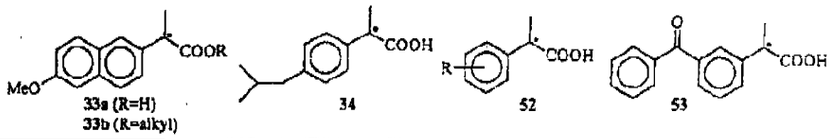
Scheme 13. Asymmetric transformation of imidazolidines.

4.2.3 Racemization of α-alkyl or -aryl substituted carboxylic acids, esters, ketones and related compounds.

Racemization of nonsteroidal antiinflammatory drugs (NSAIDS) naproxen **33a**, ibuprofen **34**, hydratropic acid **52** (R=H) and ketoprofen **53** are collected in table 6. A general method to racemize these compounds is by heating with hydroxides (entry 1,5,9,11,14) or amines in inert solvents (entry 1,2,8). Naproxen **33a** and ibuprofen **34** can be racemized in a saturated NaOCl-solution, in which NaOCl probably acts as a base (entry 4). The unwanted isomer of naproxen in resolution processes can be epimerized by

heating the salt of naproxen and an optically active amine in the mother liquid (entry 6,7,10). Profens can also be racemized by in situ conversion into a mixed anhydride under basic conditions (entry 3,12) or by heating with a strong basic ion exchange resin (entry 13).

Table 6. Racemization of Profens

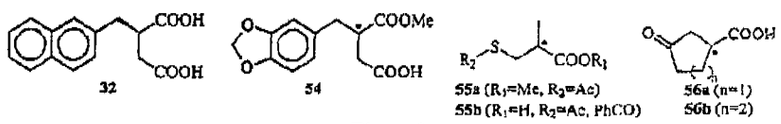


33a (R=H) 33b (R=alkyl) | 34 | 52 | 53

Entry	Compound	Racemization conditions	Yield (%)[a]	Ref
1	**34**	NaOH/2-propanol or Et_3N/octane, reflux, 15 h	n.r.	112
2	**34**	Et_3N, H_2O, 1% MBA, ΔP, 120°C, 4h	n.r.	113
3	**34**	0.1 eq. Ac_2O, NaOAc, iPrOAc, reflux, 18 h	n.r.	114
4	**33a, 34**	saturated NaOCL-solution, H_2O, 80°C, 1-24 h	>90	115
5	**33a**	NaOH, KOH, H_2O, heating	n.r.	116
6	**33a**	heating mother liquid of resolution with optically active amine in DMF/H_2O=95/5, 115°C, 24 h	n.r.	117
7	**33a**	heating mother liquid of resolution with 1-*p*-tolyl-ethylamine, autoclave, 150°C, N_2, 12 h	>90	118
8	**33a**	DBU, DBN or DABCO in inert polar solvent, 80-100°C, 3-9 h	>90	119
9	**33a**	NaOH, KOH, NaOR, KOR, inert polar solvent, T>100°C, >24 h	>90	120
10	**33a**	heating mother liquid of resolution with MBA, inert solvent, 80-150°C, 5-48 h	n.r.	121
11	**33b**	NaOH, KOH, 2-ethoxy-ethanol, reflux, 5 h	95	122
12	**52** (R=H)	Ac_2O, pyridine, reflux	n.r.	123
13	**52**	strong basic ion exchange resin, anhydrous	n.r.	124
14	**53**	NaOH, methylisobutylketon, 70-100°C	n.r.	125

a) n.r. = not reported.

A crystallization-induced asymmetric transformation was achieved with the methyl and ethyl esters of naproxen **33b**, which form conglomerates. In a supersaturated solution of **33b** and a base (*e.g.* NaOEt, DBU, DBN) in ethanol at 25-70°C, crystallization with seeding resulted in the isolation of optically pure (R)-**33b** with yields of 63-87%[126].



32 | 54 | 55a (R_1=Me, R_2=Ac) 55b (R_1=H, R_2=Ac, PhCO) | 56a (n=1) 56b (n=2)

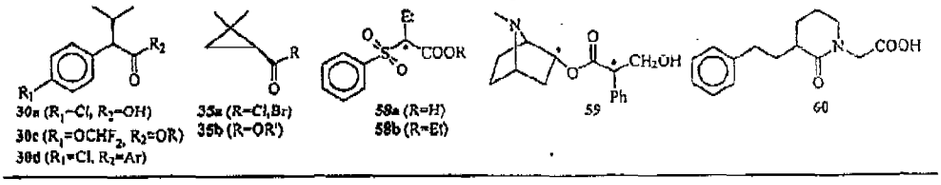
Figure 9.

2-Aryl-succinic acid derivatives **32** and **54** are racemized by initial conversion to their dimethyl esters. Subsequent heating with NaOMe in MeOH at reflux for several hours results in the racemic di-esters which are finally hydrolyzed to the racemic acids[127].

Racemization of methyl S-acetyl-β-mercaptoisobutyrate **55a** is difficult due to its decomposition. The reaction was performed by DBU, DBN or DABCO at 50-100°C for 5-10 h in solutions of methyl methacrylate and DMF to suppress the retro-Michael reaction and results in racemic **55a** in varying yields[128]. Mercaptoisobutyric acid derivative **55b** was racemized by DBN/NaOAc in refluxing xylene for 1.5 h in a yield of 80-90%[129].

Racemization of 3-oxo-cyclopentanoic acid **56a** and 3-oxo-cyclohexanoic acid **56b** was carried out by initial conversion to the methyl esters, treating the esters with NaOMe at reflux for 2 h followed by hydrolysis to the racemic acids. The racemic acids were obtained in yields exceeding 90%[130]. Racemizations of other α-alkyl substituted carboxyl derivatives are summarized in table 7.

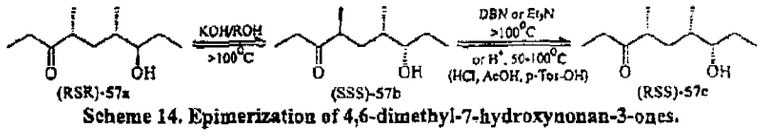
Table 7. Racemization of α-Alkyl or -Aryl Substituted Carboxylic Acids, Esters, Ketones and Related Compounds.



Entry	Compound	Racemization conditions	Yield (%)[a]	Ref
1	**30a**	50% aqueous KOH solution, 136°C, 5 h.	98	131
2	**30c**	alkali metal hydroxides, anhydrous alcohol solutions, 60-100°C	90	132
3	**30d**	DBU and DABCO	n.r.	133
4	**35b**	alkali metal hydrides or alkali metal alkoxides, 20-200°C	n.r.	134,135
5	**58a**	half-life $t_{½}$=1350 h (EtOH, 27°C)	n.r.	136
6	**58b**	$t_{½}$=80 h (EtOH, 27°C), $t_{½}$=24 h (EtOH, 47°C)	n.r.	136
7	**58b**	NaOEt, EtOH, -10°C	n.r.	136
8	**59**	amine, heating, organic solvent	n.r.	137
9	**60**	heating mother liquid of resolution with quinine, NaOEt in IPA	n.r.	138

a) *n.r. = not reported.*

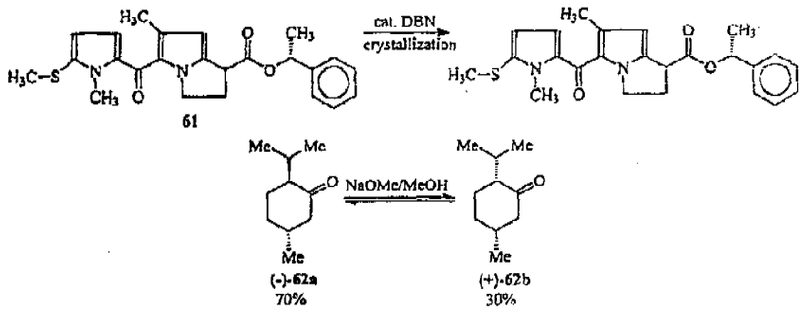
In the synthesis of 4,6-dimethyl-7-hydroxy-nonan-3-ones 57 four diastereomers are obtained from which only diastereomer **57b** (S,S,S) shows sex attraction activity. The unwanted diastereomer **57a** can be epimerized with KOH or NaOH and **57c** with DBN, Et_3N or acid at temperatures around 100°C. The obtained diastereomeric mixtures can be separated by column chromatography (scheme 14)[139].



Scheme 14. Epimerization of 4,6-dimethyl-7-hydroxynonan-3-ones.

A crystallization-induced asymmetric transformation was observed with covalent diastereomers of **61** (scheme 15). In situ epimerization is induced by a catalytic amount of DBN at 25-60°C in a mixture of EtOAc/Hexane, and under crystallization conditions optically pure **61** is isolated and converted to the

enantiomerically pure ethyl ester, a compound with analgesic and anti-inflammatory activity[140]. A first-order asymmetric transformation could also be attained with menthone **62a** which after thermodynamic equilibration in a solution of NaOMe/MeOH gives an excess of (-)-62b[141].



Scheme 15.

A study of the solvent control in the racemization of nitriles **63** and **64** and their amide and ester analogues showed a large increase in the racemization rate (~factor 10^9) going from MeOH to DMSO. The kinetics of these reactions were studied by hydrogen-deuterium exchange[60a] and the results were explained by different solvation of the base and the substrate in the solvents used. A similar study of the isotope effect in the racemization of 2-phenyl-propionitrile **63** by NaOMe at 10°C showed an increasing racemization rate with increasing concentration of DMSO in DMSO/MeOH solutions[142]. A kinetic isotope study of nitriles **63** and **65** in the reaction with bases KOMe and KOtBu in deuterated methanol, tertiary butyl alcohol and DMSO, showed either retention, inversion or racemization depending on the substrate, solvent and base used[143].

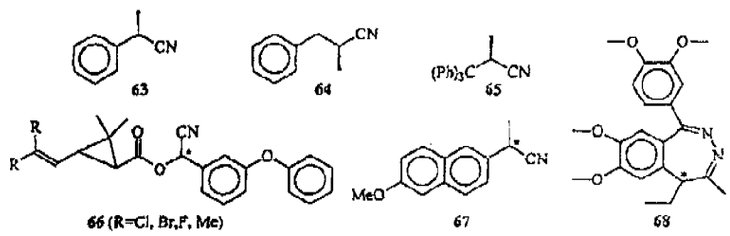


Figure 10.

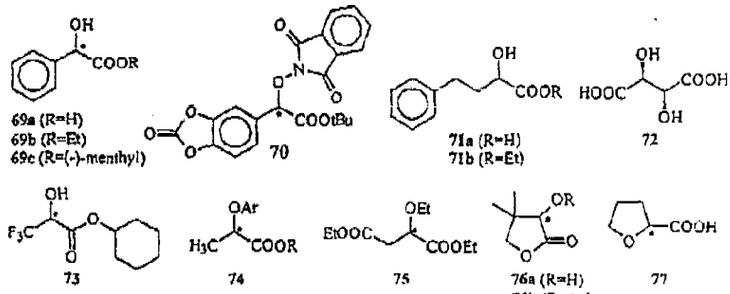
Epimerization of cyclopropanecarboxylates **66**, used as pyrethroid insecticides, at the benzyl position is induced by base (*e.g.* NH_3, Et_3N, morpholine) in aprotic polar solvents (preferably Et_3N in acetone at 20°C for 15 h). A crystallization-induced asymmetric transformation of **66** (R=Br, cis, deltamethrin) can also be achieved[144]. Epimerization of **66** can also be performed with insoluble basic catalysts (*e.g.* alumina, talc, alkali carbonate, basic ion exchange resin, CaO, MgO) in apolar or aprotic polar solvents at temperatures of -20 to 150°C. These reactions can be carried out by passing the substrate trough a column of the catalyst[145].

Racemization of the nitrile derivative of naproxen 67 is accomplished by a strong basic ion exchange resin (OH^-) in an organic solvent[146]. Tofisopam 68, a psychovegetative regulator, is partially racemized by KOtBu at 100°C[147].

4.2.4 Racemization of α-hydroxy carboxylic acids, esters, ketones and related compounds.

The racemization results of α-hydroxy carboxylic acids, esters, ketones and related compound are collected in table 8.

Table 8. Racemization of α-Hydroxy Carboxylic Acids, Esters, Ketones and Related Compounds.



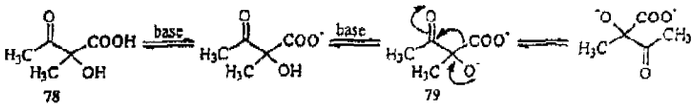
Entry	Substrate	Reaction Conditions	Yield (%)	Racemization (%)	Ref
1	**69a**	alkali metal hydroxides, water or alcohol	n.r.	100	162
2	**69b**	Na, toluene, 25°C, 5 h	44	100	148
3	**69c**	1st order asymmetric transformation, KOH/EtOH	n.r.	(S)/(R)=54/46	149
4	**(-)-70**	Et_3N, CH_3CN, 0-50°C	88	100	150
5	**(RS)-70**	2nd order asymmetric transformation, Et_2CO, DDU, 15-40°C, 3 h	80% (S)-67, 84% ee		151
6	**71a**	ΔT, base (*e.g.* NaOAc, pyridine, Et_3N), Ac_2O	n.r.	n.r.	152
7	**71b**	NaH, toluene, reflux	87	100	153
8	**72**	alkali, H_2O, reflux, 5-8 h, via meso-tartaric acid	n.r.	n.r.	154
9	**73**	PPh_3, dialkyl azo-dicarboxylate, DBU or DBN	69	100	155
10	**74**	NaOR, KOR or DBU, anhydrous inert solvents	n.r.	100	156
11	**75**	NaOEt in EtOH	n.r.	100	157
12	**76a**	NaOR, KOR, DBU, DBN, RT-120°C, with or without solvent	n.r.	100	158
13	**76a**	NaOH or KOH, 145°C	n.r.	100	159
14	**76b**	$Ba(OH)_2$, NaOMe, K_2CO_3, NaOAc, heated anhydrous solutions	> 90	100	160
15	**77**	NaOH or KOH, H_2O, 140-160°C, 5 h	90	100	161

a) n.r. = not reported

Mandelic acid **69a** was racemized by refluxing or heating with alkali metal hydroxides dissolved in water or alcohol[162]. Racemization reactions were studied in aqueous solutions at pH 1-12 at temperatures ranging from 25 to 100°C. No racemization was observed in acidic solutions (less than 11.2N at 96°C). Parameters effecting the first-order racemization constant are the temperature and concentration of base[162].

The tautomeric equilibrium of mandelic acid **69a** was studied and a pK_E of 15.4 was found for the acid and 22.0 for the carboxylate[164].

An unusual racemization is that of 2-hydroxy-2-methyl-3-one-butyric acid **78** under basic conditions which involves a tertiary ketol rearrangement of dianion **79** as shown in Scheme 16[165]. An α-ketol rearrangement is also possible for α-hydroxy aldehydes and ketones under acidic conditions[166].



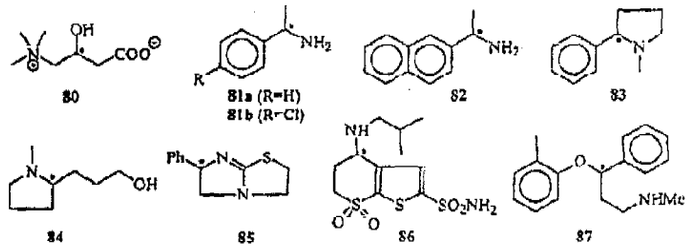
78 79

Scheme 16. Tertiary ketol rearrangement.

4.2.5 Racemization of miscellaneous compounds.

Racemizations of several chiral compounds bearing a nitrogen or an oxygen at the chiral center are summarized in table 9.

Table 9. Base-catalyzed Racemization of Compounds Bearing a Nitrogen or Oxygen at the Chiral Center.



80 81a (R=H) 81b (R=Cl) 82 83

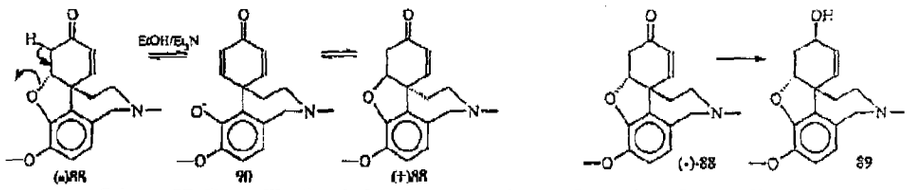
84 85 86 87

Entry	Substrate	Reaction Conditions	Yield (%)[a]	Racemization (%)	Ref
1	**80**	NaOH, NaOMe, $NaHCO_3$, Na_2CO_3, Bu_4NOH or DABCO	n.r.	100	167
2	**81a**	catalytic $NaNH_2$ or NaH, 100-140°C, without solvent	~100	100	168
3	**81b**	metal alkoxide (*e.g.* KOtBu), DMSO, RT-200°C	>90	100	169
4	**82**	NaH, KH, aromatic solvents, 50-160°C.	n.r.	n.r.	170
5	**83**	NaOR or KOR, NaH or $NaNH_2$, reflux, organic solvents	>95	100	171
6	**83**	NaOR or KOR, NaH or $NaNH_2$, without solvent	>95	100	172.
7	**84**	NaOMe in MeOH, 60-195°C	77	100	173
8	**85**	KOH in DMSO	83	100	174
9	**85**	ΔT, Bu_4NI, ethylenimine.	n.r.	100	175
10	**86**	1) acylation. 2) racemization: ΔT, formamide, NR_3, NaOR or KOR), protic solvent. 3) deacylation. 4) purification	77	100	176
11	**87**	BuLi, DME or THF, inert gas, RT	n.r.	100	177

a) n.r. = not reported

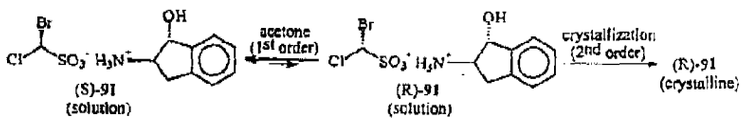
A unique epimerization at two stereocenters in one step was observed during the crystallization-induced asymmetric transformation of (-)-narwedine **88**, a compound with cardiac, analgesic and hypotensive activity.

The in situ epimerization mechanism involves a retro-Michael reaction via achiral intermediate 90. When the epimerization was carried out under crystallization conditions in a supersaturated solution and seeded with (-)-88, optically pure (-)-88 is isolated, which can be converted into (-)-galanthamine 89, an acetylcholine esterase inhibitor that can be used in the treatment of Alzheimers disease (Scheme 17)[71].



Scheme 17. Crystallization-induced asymmetric transformation of narwedine.

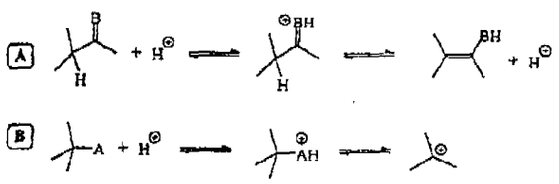
A first-order asymmetric transformation was observed for chlorobromomethanesulfonic acid 91 under influence of an optically pure aminoalcohol (scheme 18). Under equilibration conditions in acetone the diastereomers are present in a ratio of (S)-91/(R)-91=81/9. In a saturated solution of acetone, after seeding with optically pure material, crystallization of one diastereomer results and optically pure (R)-91 was isolated in 75% yield[19] (note that this is the diastereomer least present in solution).



Scheme 18. First and second-order asymmetric transformation of chlorobromomethanesulfonic acid.

4.3 Acid-catalyzed racemization

Compared to base-catalyzed racemizations the scope of acid-catalyzed racemizations is somewhat limited. Usually two pathways are recognized. The most frequently encountered pathway for acid-catalyzed racemization is the protonation of a double bonded heteroatom in an α-position to a chiral center, followed by abstraction of a hydrogen from the chiral center (scheme 19A), representing keto-enol tautomerism if the heteroatom is oxygen, and imine-enamine tautomerism for nitrogen. This mechanism is conceptually similar to base-catalyzed racemization. The protonated heteroatom enhances the acidity of the α-proton to such an extent that even a very weak base can affect deprotonation.

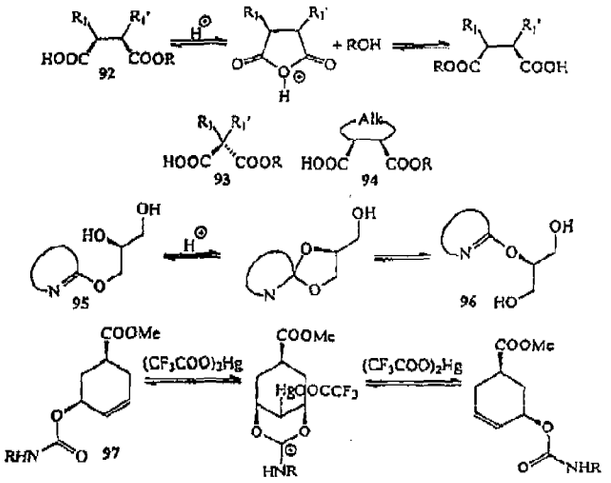


Scheme 19. Mechanisms for acid catalyzed racemization (Brønsted as well as Lewis-type acids).

Acid-catalyzed racemization is also possible if a substituent is present at a chiral center which, upon protonation, is converted into a good leaving group. This leads to the reversible formation of a carbocation which is planar (unless constrained in some manner) resulting in racemization (scheme 19B). The carbocation must be stabilized by other functionalities otherwise rearrangement can occur easily, leading to unwanted side reactions. The need for a substituent that can act as a leaving group combined with the need for a cation stabilizing functionality is more restricting than in base-catalyzed racemizations, where only an anion stabilizing group has to be present, but this mechanism is also possible with compounds lacking a hydrogen attached to the chiral center.

Although most of the acid-catalyzed racemizations proceed by one of the general mechanisms depicted in scheme 19 there are also some reactions known where no chiral center is involved, but where symmetrization is achieved in a different manner. Examples of such types of racemization are shown in scheme 20.

Dicarboxylic acid monoesters like compounds 92, 93 and 94 undergo acid-catalyzed transesterification. As these reactions proceed via a symmetrical and achiral intermediate racemization is achieved without affecting any chiral center directly[180]. Other examples of indirect acid catalyzed racemizations are the heterocyclyloxy propanediols 95 where the heterocyclic group moves between the hydroxy functions. The intermediate 96 is symmetrical, and therefore achiral. The heterocyclic group may be thiazole, pyridine, pyrazine or pyrimidine[181]. Compound 97 also epimerizes via a symmetrical intermediate, but here one of the chiral centers is stereoselectively rearranged under the influence of mercuric trifluoracetate acting as a Lewis acid[182]. Other examples of racemizations which do not affect the chiral center can be found in sections 4.7.1 and 4.7.2.



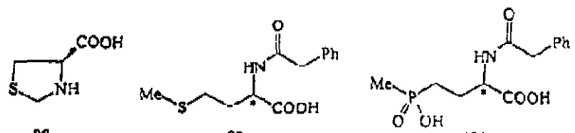
Scheme 20. Indirect acid catalyzed racemizations.

4.3.1 Racemization of amino acids and related compounds.

Acid-catalyzed racemization of amino acids is probably the most extensively studied type of racemization. The reason is that amino acids can be very easily racemized (according to the general approach shown in scheme 19A), after *in-situ* conversion to imines (Schiff bases)[183] using a wide variety of aldehydes and ketones. This method is of major importance for the industrial synthesis of optically pure amino acids and is treated in detail in section 4.4.

Most, if not all, free amino-acids can be racemized under acidic conditions. The dependence of the rate of racemization on the pH has been studied and turned out to be complex, *viz.* depending on no less than six rate constants[91,184]. Acid-catalyzed racemization requires strong acids and temperatures well above 100°C. Racemization of alanine, valine, leucine and phenylalanine at 142°C proceeds slowest at pH's between 1 and 3[184]. Some examples of this method are collected in table 10. Esterification of the acid, or transforming the amine into an amide are routinely applied methods to facilitate the racemization under acidic conditions (see table 10).

Table 10. Acid-catalyzed Racemization of Amino Acids and Related Compounds.

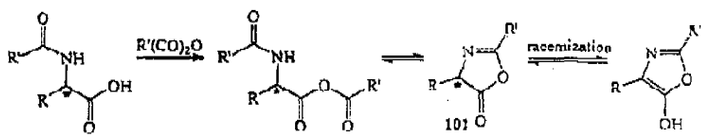


98 99 100

Entry	Amino Acid	Conditions	Results[a]	Ref.
1	Phenylglycine	$PhSO_3H$ (20% in water), 160°C, 6h	n.r.	185
2	Lysine	Aqueous HCl (10%), 170°C, 4h	n.r.	186
3	Cysteine	Aqueous HCl (6N), 120-140°C, 24h	81.5%	187
4	S-carboxymethyl cysteine	Aqueous HCl (35%), 130°C, 30h	95%	188
5	Cystine	Aqueous HBr (48%), heating, 40-45h	10%[b]	189
6	**98**	Acetic acid (99.5%), reflux, 2h	45%	190
7	Phenylglycine methyl ester	H_2SO_4, 160°C, 5h	80-90%	191
8	**99**	Phenylacetic acid, 180°C, 5-10min.	90%	192
9	**100**	H_3PO_4, 100°C, 45 min.	95%	193

a) n.r. = not reported. b) Gives mixture of DL and meso-cystine, and after reduction 10% DL-cysteine

N-Acyl amino acids are often racemized in the presence of anhydrides or ketenes. The in-situ formation of azlactones **101** (scheme 21), which racemize readily under acidic conditions, greatly facilitates



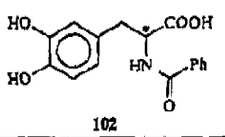
101

Scheme 21. Formation of azlactones from N-acyl amino acids.

racemization. The ease of racemization of azlactones is mainly due to the formation of an aromatic ring system. Often an anhydride is formed which has to be hydrolyzed subsequently with an aqueous base. The

use of relatively large amounts of anhydride and the formation of salts makes this reaction somewhat less attractive from an industrial viewpoint. The data in table 11 reveal that the conditions for racemization of N-acyl amino acids in the presence of anhydride are much milder than those for unprotected amino acids.

Table 11. Racemization of N-acetyl Amino Acids in the Presence of Anhydrides.



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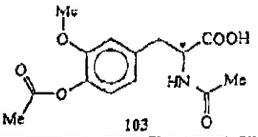

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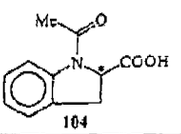
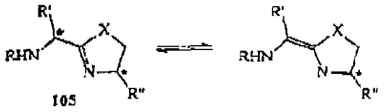


104

Entry	Amino acid	conditions	Results[a]	Ref.
1	N-acetyl methionine	Ac_2O (cat.), 120°C (melt)	99.1%	194
2	N-acetyl phenylglycine	Ac_2O / AcOH (cat.), 160°C	95%	195
3	**100**	Ac_2O / AcOH, 115°C, 30min.	96%	196
4	**102**	Ac_2O, 80°C, 45min.	93%	197
5	**103**	Ac_2O / AcOH	n.r.	198
6	**104**	Ac_2O / AcOH, 95°C, 6h	97%	199
7	N-acetyl phenylalanine	Ketene, aqueous solution pH 4-7, 70-90°C	n.r.	200

a) n.r. = not reported

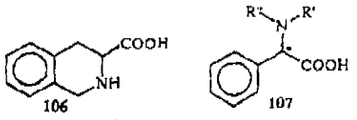
Cyclic derivatives of amino acids such as **105**, *i.e.* imidazolidines (X=N), oxazolidines (X=O) and thiazolines (X=S) racemize or epimerize, very easily under acid and basic conditions (scheme 22)[201]. In



105

Scheme 22.

principle asymmetric transformations are conceivable for amino acids if chiral acids of sufficient acid strength are available. However, most chiral acids are incapable of directly racemizing amino acids at temperatures which allow the crystallization of the salt and only a few examples of this type of asymmetric transformation are known. N-Acyl derivatives of proline, leucine and phenylglycine can be obtained with ee's ranging from 40 to 90% by preferential crystallization from the melt in the presence of a catalytic amount of acetic anhydride[202].



106 107

Figure 11.

A crystallization-induced asymmetric transformation is possible for compounds **106** and **107** (R'=H, R''=Me; R'=H, R''=Et or R'=R''=Me) with camphorsulfonic acid as resolving agent, using high boiling, relatively apolar, carboxylic acids such as propanoic-, butanoic- and hexanoic acid as the solvent. At

temperatures between 90 and 120°C racemization proceeds at an acceptable rate and the solubility of one of the diastereomeric salts is sufficiently low. The yields of these asymmetric transformations vary between 75 and 100% with ee's ranging from 85 to 100%[203] (additional examples are collected in section 4.4).

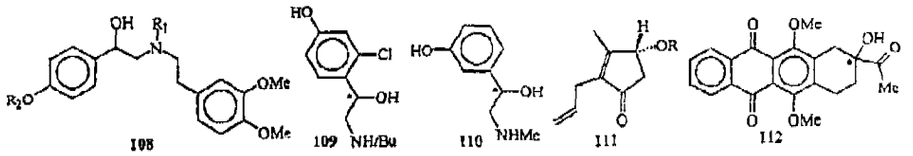


Figure 12. Racemization of hydroxy-compounds.

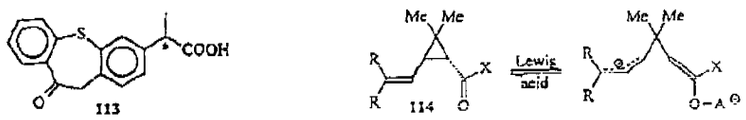
4.3.2 Racemization of hydroxy-compounds.

Compounds with a hydroxy function attached to a chiral center may be racemized following the mechanism shown in scheme 19B. In practice however this type of reaction is not often found. Unwanted side reactions can be prevented only if the intermediat[illegible]bocation is sufficiently stabilized or is unable to undergo rearrangement. This is the case for the examples given in figure 12. The racemization of compounds **108**[204], **109**[205] and **110**[206] requires relatively mild conditions, *i.e.* dilute acids or ion-exchange resin[207] and temperatures between 40 to 130°C. Compound **111** (R=H) which is a constituent of allethrin insecticides can be racemized by in refluxing formic acid, containing [illegible]ll amount of water for 48h[208]. This leads to the formation of optically inactive formate which subsequen[illegible] has to be hydrolyzed. Compound **111** can also be racemized by treatment with PBr_3 to give the bromide (R=Br)[209], or with PCl_3 or PCl_5 in the presence of a Lewis acid ($ZnCl_2$ or BF_3) to give the chloride (R=Cl)[210], which can be transformed into the optically inactive hydroxy compound by treatment with hydroxide.

Compounds with the hydroxy group adjacent to a carbonyl moiety are rather racemized by keto-enol tautomerism than by the formation of a carbocation. 4-Demethoxy-7-deoxydaunomicinone can be racemized with p-toluenesulfonic acid after conversion into the dimethylether **112**[211]. Mandelic acid **69a** could be partially racemized by treatment with talc, which has acidic as well as basic sites[212]. D-Tartaric acid **72** was racemized in the presence of meso-tartaric acid to give 74% of DL-tartaric acid. In the absence of the meso acid only 50% racemization was observed[213].

4.3.3. Racemization of miscellaneous compounds.

α-Alkyl α-aryl acetic acids can be racemized under acid conditions. Dibenzothiepine **113** racemizes in acetic acid with 4N HCl at 140°C in 12 hours giving a nearly quantitative yield (scheme 23)[214]. Carboxylic acid **30a** (table 2) racemizes in the melt in the presence of a catalytic amount of sulfuric acid (140°C, 2h) or p-toluenesulfonic acid (220°C, 1h)[215] and naproxen **33a** (table 2) can be racemized by refluxing in acetic anhydride[216].



Scheme 23. Racemization of Dibenzothiepine and Chrysanthemic acid derivatives.

Chrysanthemic acid and related compounds are intermediates in the synthesis of important insecticidal pyrethrins[217]. As only one enantiomer shows high activity and environmental regulations requires the sole use of this enantiomer the enantioselective preparation is of industrial importance[218]. Racemization of chrysanthemic acid derivatives **114** (R=Alkyl; X=Cl, Br or anhydride) with Lewis acids proceeds by opening of the central cyclopropane bond which leads to the simultaneous inversion of both chiral centers of the cyclopropane moiety (scheme 23)[219]. A noteworthy feature of this type of racemization is the use of Lewis acids; as in most acid-catalyzed racemizations Brønsted acids are applied. The conditions for this racemization are mild, requiring temperatures between 0°C and 100°C and reaction times of minutes to a few hours[220]. The reaction leads mainly to the racemic trans-isomer with only 5-10% of the racemic cis-isomer. The dichloro compound **114** (R=X=Cl) could be racemized using BI_3 at 100°C for 8h, but here the racemization was only partial[221]. Racemization of chrysanthemic acid derivatives is also possible by a similar, radical initiated, mechanism. Chrysanthemic acid, its esters, anhydrides and acid halides racemize easily upon treatment with bromides (HBr, $AlBr_3$, BBr_3, PBr_3) in the presence of an organic peroxide, an azo compound or oxygen. The reaction proceeds at low temperatures (-30°C to room temperature) and also gives small amounts of the cis-isomer[222]. The reaction can also be initiated photochemically[223].

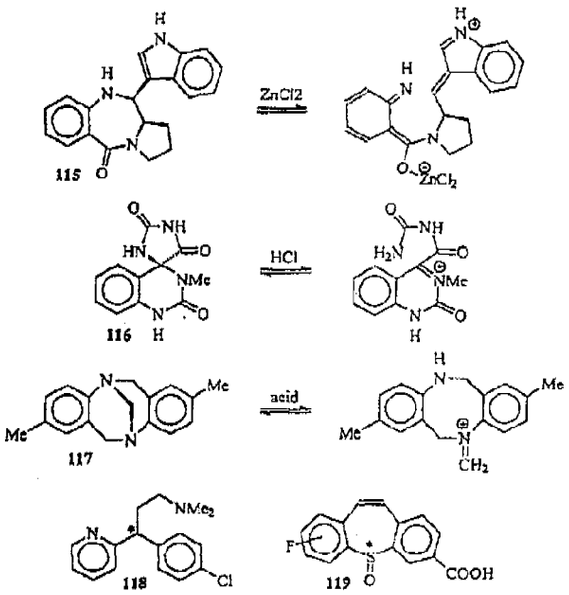


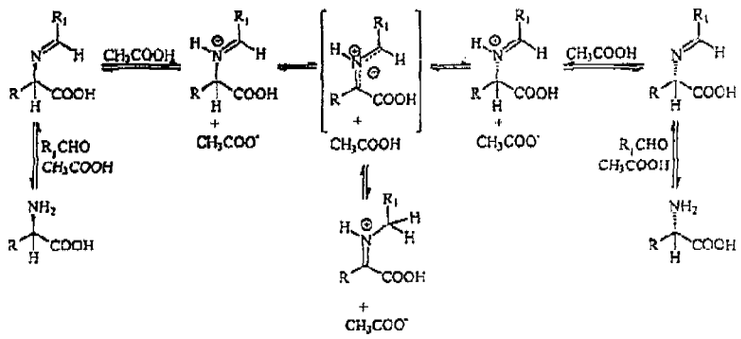
Figure 13.

Tilivalline **115** (figure 13) epimerizes under the influence of a Lewis acid (50-55°C, 24h). Racemization of compound **116** (10% HCl, 90°C, 3h)[224] and Tröger's base **117** was achieved by opening of their ring systems[225]. With Tröger's base use of a chiral cyclic phosphoric acid leads to an asymmetric transformation with an ee exceeding 95% in 93% yield[226]. The dinitrobenzoic salt of amine **118** racemizes upon heating to

160°C for 30 min[227]. Chiral sulfoxide **119** can be racemized by treatment with trifluoroacetic anhydride[228]. Finally it should be mentioned that halogen substituted carboxylic acids such as 2-chloro or 2-bromopropionic acid can be racemized by simple heating at their boiling point[229].

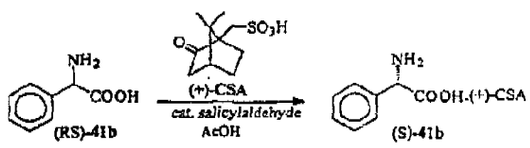
4.4 Racemization and crystallization-induced asymmetric transformation via Schiff bases.

Derivatization of a functional group connected to a chiral center is a well known method to affect optical stability. The increased leaving ability of an exchangeable group or the enhanced acidity of an attached proton allows mild racemization conditions which can often be combined with a resolution process. The aldehyde or ketone catalyzed racemization of amino acids and derivatives *via* Schiff base intermediates is the most prominent example of this method, and proceeds by initial protonation of the imine followed by proton abstraction by the acetate anion (scheme 24). This mechanism was confirmed by kinetic studies of the hydrogen-deuterium exchange of Schiff bases[230].

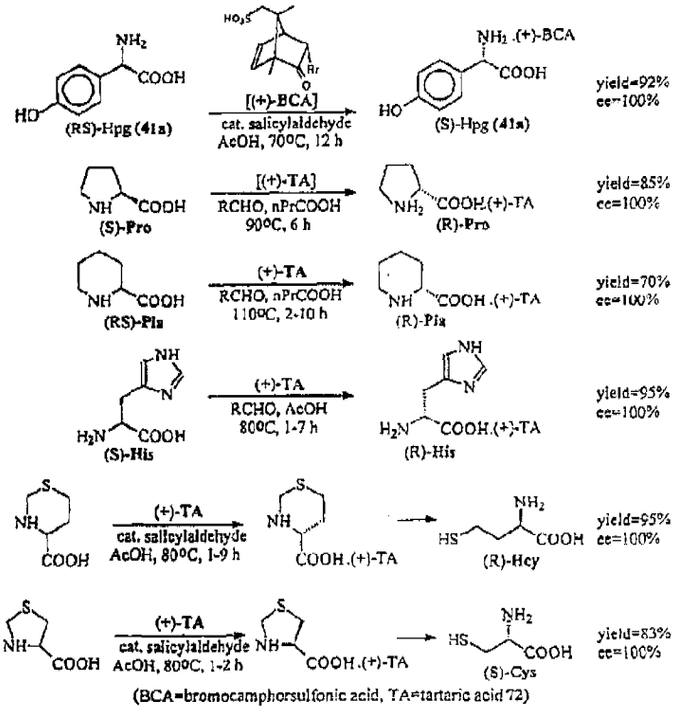


Scheme 24. Racemization of amino acids via Schiff bases.

More than 100 patents (not including equivalents) have described a combination of Schiff base-promoted racemization with a resolution process by selective crystallization, thus affecting an crystallization-induced asymmetric transformation. Well known examples are the asymmetric transformation of phenylglycine **41b** using camphorsulfonic acid (CSA) and salicylaldehyde in acetic acid resulting in the isolation of optically pure **41b** in 70% as described by Yamada and Hongo (scheme 25)[231]. Some other very efficient examples of crystallization-induced asymmetric transformations of amino acids are shown in scheme 26.



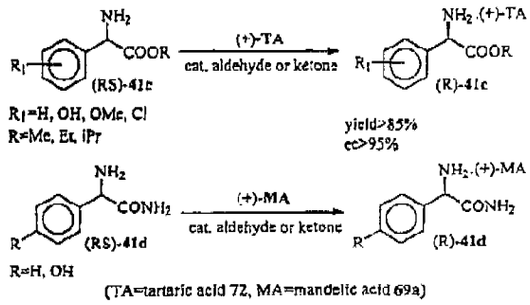
Scheme 25. Crystallization-induced asymmetric transformation of phenylglycine.



(BCA=bromocamphorsulfonic acid, TA=tartaric acid 72)

Scheme 26. Crystallization-induced asymmetric transformation of amino acids.

In the synthesis of aspoxicillen, two crystallization-induced asymmetric transformations to optically pure D-*p*-hydroxy-phenylglycine (Hpg) **41a** and D-aspartic acid (Asp) are used with yields exceeding 90%. This method is very attractive because the same resolving agent (phenylethanesulfonic acid, PES) is used[232].



(TA=tartaric acid 72, MA=mandelic acid 69a)

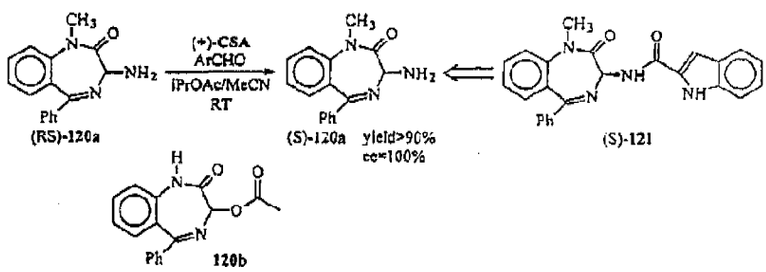
Scheme 27. Crystallization-induced asymmetric transformation of amino acid esters and amides.

Also amino acid derivatives like simple esters **41c** and amides **41d** can successfully be applied as shown by work of DSM[233] and Glaxo[230] respectively (scheme 27).

A more detailed survey of the patent and scientific literature shows that virtually every amino acid has been used in a Schiff base-promoted racemization or crystallization-induced asymmetric transformation. A comprehensive survey is given in Table 12 and Table 13. In more general terms the method is characterized by:

- all amino acids and simple esters or amides can be used provided an α-proton is present and the amino-group is not protected.
- for Schiff base formation aromatic aldehydes like salicylaldehyde or pyridoxal are preferred but also aliphatic aldehydes and even simple ketones can be used.
- in most examples a catalytic amount of aldehyde (1-10%) is sufficient; an excess is often used for other reasons.
- the aldehyde (or ketone) can also be used as solvent or co-solvent.
- the aldehyde can be activated by additional substituents *i.e.* nitro-groups in aromatic aldehydes or made water soluble through sulfonic acid functions.
- immobilization of the aldehyde can be used to simplify down stream processing.
- in most cases additional acid or base is used to set up the required equilibrium system.
- resolving acids as well as bases can be applied together with the racemization catalyst.
- simple solvents like water, acetic acid, alcohols and ketones can be used; preferably one of the reactants is used in excess to serve as solvent.
- reaction conditions are mostly mild using reflux (50-100°C) and high concentrations (5-20%).
- yields are generally good to excellent (70-100%).

A quantitative analysis of crystallization-induced asymmetric transformations of phenylglycines (Phg) and phenylglycinates **41** showed that the racemic substrate, solvent and carbonyl compound are of equal importance in affecting an crystallization-induced asymmetric transformation[234].



Scheme 28. Schiff base-catalyzed racemization and asymmetric transformation of benzodiazepinones.

An example of a crystallization-induced asymmetric transformation of an amino acid related compound is shown in the synthesis of CCK-antogonist **121**. Here a Schiff base-catalyzed crystallization-induced asymmetric transformation of benzodiazepinone **120a** is used and results in the isolation of optically pure **120a** in more than 90% (scheme 28)[235]. A base-catalyzed racemization is observed for 3-O-acyloxazepam

120b, which in fact is a Schiff base. This racemization was studied by deuterium-exchange experiments and it was found that racemization occurred via a keto-enol mechanism at pH 7-14[236].

Table 12. Survey of Schiff Base Promoted Racemization and Crystallization-induced Asymmetric Transformation of Amino Acids

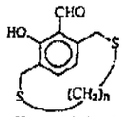
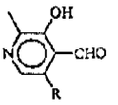
Entry	Amino acid	Aldehyde or Ketone	Reaction Conditions	Results	Ref
1	L-Ser	pyridoxal, salicylaldehyde	H_2O, pH 13, 48 h, 60°C	DL 90-100%	237
2	L-Ser	CH_3CHO	Cu(II)/NaOH	DL-Ser	238
3	L-Lys	pyridoxal, salicylaldehyde	H_2O, NH_4OH, 100 h, 50°C	DL-Lys 80%	239
4	DL-Hpg	salicylaldehyde	H_2O, AcOH, (+)-bromocamphorsulfonic acid	D-Hpg 92%, 99% ee	240
5	DL-Hpg	ArCHO	H_2O, H^+	D-Hpg, 99%	241
6	DL-Hpg	various aldehydes	CH_3CN, (+)-phenylethanesulfonic acid	D-Hpg 99%	232, 242
7	DL-Hpg	various aldehydes	AcOH, Ac_2O, sulfonic acids, 30 h, 100°C	D-Hpg 70%, 97% ee	243
7	DL-Phg	salicylaldehyde	AcOH, (+)-camphorsulfonic acid	L-Phg 70%, 100% ee	231
8	DL-Ala	various aldehydes	AcOH, Ac_2O, sulfonic acids, 30 h, 100°C	D-Ala 16%, 98% ee	231c
9	L-Pro	butanal	butanoic acid, tartaric acid, 80°C	D-Pro 85%, 100 % ee	244
10	DL-Pia	butanal	butanoic acid, tartaric acid, 80°C	D-Pia, 70%, 100% ee	244b
11	L-His	salicylaldehyde	AcOH, tartaric acid, 80°C	D-His, 95%, 100% ee	245
12	L-Isoleu	salicylaldehyde	AcOH, H_2O, 100°C	DL, 90%	246
13	Phg	pyridoxal	phosphate buffer	DL	247
14	DL-DOPA	salicylaldehyde	AcOH, H_2O, 3 h, 92°C, seeding	L-DOPA, low yields	248
15	L-Ac-Cys	salicylaldehyde	H_2O, H^+, reflux, 12 h	DL, 85%	249
16	DL-Cys DL-Hcy	various aldehydes	AcOH, tartaric acid, via 4-thiazolidinecarboxylic acid or 1,3-thiazane-4-carboxylic acid	D-Cys or D-Hcy, 80-90%, 100% ee	250
17	various	5-NO_2-salicylaldehyde	H_2O, tBuOH, quinine, reflux	asymmetric transformation	251
18	various	various aldehydes	AcOH, 1 h, 80-100°C	DL,86-92%	231b, 252
19	various	various ketones	H^+ or $AlCl_3$, 60-160°C	DL	253
20	various	various ketones	organic acid	DL	254
21	various	glyoxylic acid	H_2O, $AlCl_3$, reflux	DL	255
22	various			DL	256
23	various	salicylaldehyde	H_2O, Al-silicate, Al_2O_3 or Cu(II), 80-100°C	DL	257
24	various	ArCHO bound to a carrier or resin	various solvents, RT-100°C	DL	258

Table 13. Survey of Schiff Base Promoted Racemization and Crystallization-induced Asymmetric Transformation of Amino Acid Derivatives

Entry	Amino acid derivative	Aldehyde or Ketone	Reaction Conditions	Results	Ref
1	DL-Phg-esters	various aldehydes or ketones	ROH, RT (+)-tartaric acid	D-Phg esters, 95%, 100% ee	230
2	DL-Hpg-esters	various aldehydes or ketones	ROH, RT (+)-tartaric acid	D-Hpg-esters, 95%, 100% ee	230
3	L-Phe-OMe	pyridoxals	50-300°C, H_2O	DL	259
4	various esters	 R=$CH_2SCH_2COO^-$ $CH_2OPO_3^{2-}$	alcohol, DMF or H_2O, pH 5-10 0-50°C	DL	260
5	various amides	pyridoxal phosphoric acid	H_2O, metal ions, 0-200°C	DL	261
6	L-Phg-amides	acetone	AcOH, H_2O, reflux, 24 h	DL, 94%	262
7	D-Phg-amides	PhCHO	EtOAc, Toluene, H_2O, 85°C, 4 h	DL, 94%	263
8	various amides	PhCHO	acetone, KOH, H_2O, 20-60°C, 19 h.	DL	264
9	DL-Phg-amides	PhCHO	L-mandelic acid	D-Phg-amides,	233
10	DL-Hpg-amides	PhCHO	L-mandelic acid	D-Hpg-amides	233

Related methods for amino acid racemization and asymmetric transformation are generally less efficient. Hydantoins[265] **49**, azlactones[266] **101**, diketopiperazines[267] and other amino acid derivatives have been used (see also section 4.2.2 and 4.3.1). In all these derivatives the acidity of the α-proton is enhanced. Hydantoins are particularly well suited for asymmetric transformation as most hydantoins (*i.e.* with aromatic substituents) racemize spontaneously under resolution conditions. Drawback of these methods are the need to prepare and isolate the amino acid derivatives and/or the stoichiometric reaction conditions.

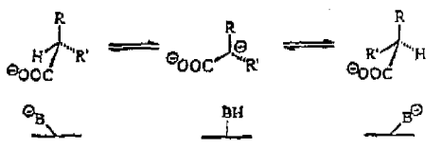
4.5 Enzyme-catalyzed racemizations

An increasing number of enzymes and related biocatalytic systems are reported which affect racemization, sometimes in combination with a resolution resulting in dynamic kinetic resolutions. The substrates used in these reactions have two common features:

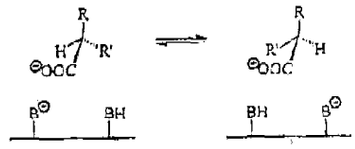
- the chiral center bears a proton.
- adjacent to the chiral center is a carbonyl group or a related acidity enhancing substituent.

Amino acids, α-hydroxy acids and related structures cover almost all enzymatic examples known to date. The enzymes, mostly known as racemases, often need a cofactor like pyridoxyl phosphate or a bivalent metal ion to function properly. As far as investigated the enzymes accept both enantiomers as substrate.

A classification according to reaction mechanism has been given by Gallo, Tanner and Knowles[268]. Depending on the number of bases at the active site involved in the racemization a 'one-base system' or a 'two-base system' can be distinguished (scheme 29 and scheme 30).

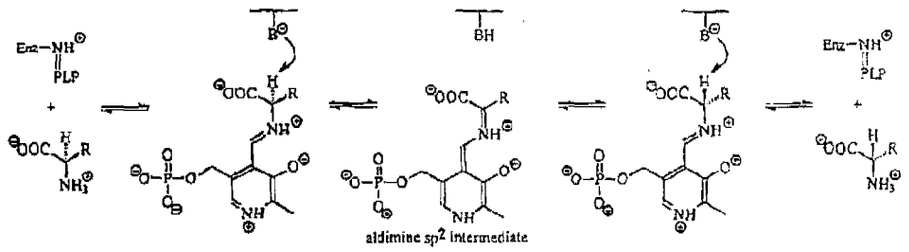


Scheme 29. 'One-base system'



Scheme 30. 'Two-base system'

Positively identified 'one-base' enzymes are α-amino-ε-caprolactam racemase, various alanine racemases and probably also the racemases for arginine, threonine and serine. They need pyridoxyl phosphate (PLP) as cofactor. PLP is used to form a Schiff base with the amino group enhancing the acidity of the adjacent proton (scheme 31)[269]; in fact this is the same mechanism as given in section 4.4. Identified 'two-base' racemases are proline, mandelic acid, aspartic acid and glutamic acid racemase. They do not need PLP as cofactor[269]. Related enzymes are the hydantoin racemases and the racemase for 2-oxothiazolidine-4-carboxylate. The precise mechanism of the 'two-base system', concerted or stepwise, is still a matter of debate[270].



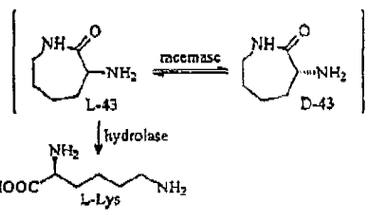
Scheme 31. Pyridoxyl phosphate (PLP)-catalyzed racemization of amino acids.

A useful classification is not an easy task. The nomenclature of the various racemases is rather erratic and sometimes misleading. Often the racemase is named after the first substrate studied, not necessary the most suitable substrate. Various racemases and their substrates are collected in table 14 which covers the main part of the reports about this racemization technique. A brief description of these racemases is described in the following notes. The best studied racemases are collected in entries 1-8. Together with modern immobilization techniques these enzymes could be valuable tools in the industrial preparation of amino acids and derivatives, in particular amino acids not available through fermentation.

Table 14. Racemases and Their Substrates.

Entry	Racemase	Substrates
1	α-Amino-ε-caprolactam (ACR)	ACR 43, α-amino-δ-valerolactone
2	Mandelic acid	(substituted) mandelic acid 69, 2-hydroxy-but-3-ene
3	Hydantoin	substituted hydantoins
4	Alanine	4 amino acids
5	Threonine	18 amino acid derivatives
6	Arginine	15 amino acid derivatives
7	*Pseudomonas Putida*	12 amino acid derivatives
8	N-Acyl-amino acid	18 N-acyl-amino acids
9	aminobutyric acid	aminobutyric acid
10	Aspartic acid	aspartic and cysteic acid
11	Proline	proline (derivatives)
12	Glutamic acid	glutamic acid
13	Sulfur containing amino acids	cystine[271], homocysteine[272], methionine[273] and selenium analogues[274].
14	*Flavobacterium*	lysine and arginine[275]
15	Serine	serine
16	Miscellaneous	miscellaneous

1. ACR racemase has been isolated from four bacterial sources and played an important role in the industrial production of lysine (Scheme 32)[276]. A wide range of substrates have been tested with ACR racemase of which only α-amino-δ-valerolactone was found to be compatible; in fact better than ACR[277].



Scheme 32. Racemase and hydrolase-induced dynamic kinetic resolution of ACR to L-lysine.

2. Mandelate racemase is isolated from *Pseudomonas putida*. This racemase is rather stable, easy to isolate and has therefore been studied in detail[278]. A divalent metal ion, preferably Mg is indispensable for optimal activity. Substrate specificity is limited. Substituents in the phenyl ring are accepted, although no more than one is allowed. Lactic acids are not accepted, but 2-hydroxy-but-3-ene carboxylic acid is a suitable substrate[279]. Reaction mechanism and crystal structures have been studied recently[270b,280].
3. Hydantoin racemase[281] is isolated from *Arthrobacter* and shows a high activity toward 5-substituted hydantoins **49a**[211] with R is alkyl or aryl (Figure 14). 5-Aryl-substituted hydantoins **49b** are not affected, however they racemize spontaneously under the usual hydantoinase catalyzed kinetic resolution (see previous section).

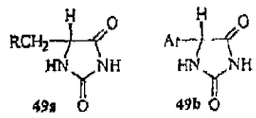


Figure 14. 5-Substituted hydantoins.

4. Alanine racemases have been isolated from four different bacterial sources and are described in some detail in the literature[282]. Most alanine racemases are not suitable for other amino acids with a notable exception of *Salmonella typhimurium* (*alr* gen.)[283] (table 15).

Table 15. Relative Activity of alanine racemase from *Salmonella typhimurium* (*alr* gen.)[283].

Substrate	Relative Activity (%)
L-alanine	100
D-Alanine	93
L-Cysteine	6.3
L-Homoserine	29
L-Serine	66

5. Threonine racemase (epimerase) isolated from *Pseudomonas putida* has a rather broad substrate specificity of which many are better than threonine (table 16)[284].

Table 16. Relative Activity of Threonine Racemase for Various Substrates[284].

Substrate	Relative Activity (%)	Substrate	Relative Activity (%)
L-Lysine	100	L-Asparagine	12
L-Ornithine	80	L-Alanine	6
L-Ethionine	83	L-Serine	10
L-Arginine	79	L-Histidine	6
L-Glutamine	54	L-Isoleucine	0
L-Methionine	66	L-Cysteine	0
S-Me-L-Cysteine	3	L-Threonine	3
ε-N-Ac-L-Lysine	75	L-Valine	0
L-Homocitrulline	45	L-Proline	0
L-Citrulline	45	L-Glutamic acid	0
L-Homoarginine	24	L-Aspartic acid	0
L-Norleucine	45	L-Tyrosine	0
L-Leucine	10	L-Tryptophane	0
L-Homoserine	22	L-Phenylalanine	0

6. Arginine racemase is isolated from *Pseudomonas graveolins* and shows a broad substrate specificity. Lysine is the preferred substrate (table 17)[285].

Table 17. Relative Activity of Arginine Racemase for Various Substrates[285].

Substrate	Relative Activity (%)	Substrate	Relative Activity (%)
L-Lysine	110	L-Ethionine	13
Arginine	100	L-Citrulline	13
ε-N-Ac-L-Lysine	86	L-Homocitrulline	12
Ornithine	44	δ-N-Ac-L-Ornithine	12
2,3-Diaminopropionic acid	40	L-Theanine	11
L-Homoarginine	25	L-Glutamine	7
L-Canavanine	19	L-Methionine	4
D-2,4-Diaminobutyrate	18		

7. Early work by Soda and Osumi resulted in isolation and characterization of an amino acid racemase isolated from *Pseudomonas putida* with a rather broad specificity (Table 18)[287]. Two moles of PLP per mole enzyme are required for efficient racemization. *Pseudomonas putida SCRC-744* racemizes phenylalanine[288].

Table 18. Relative Activity of *Pseudomonas Putida* for Various Substrates[287] (pH=8.3, $4 \cdot 10^{-4}$M).

Substrate	Relative Activity (%)	Substrate	Relative Activity (%)
D-Lysine	100	L-α-aminobutyrate	4.7
L-Ethionine	76	L-Leucine	3
D-Arginine	60	L-Histidine	1.8
L-Methionine	48	D-Glutamic acid	0
L-Citrulline	16	L-Isoleucine	0
D-2,4-Diaminobutyrate	10	L-Phenylalanine	0
L-Alanine	9	L-Threonine	0
L-Serine	8.7	L-Valine	0

8. N-Acylamino acid racemase is isolated from *Streptomyces atratus* and only active for N-acylated amino acids[256]. Bivalent metal ions enhance the activity which is quite wide (Table 19).
9. Isoleucine producing bacteria convert racemic α-amino-butyric acid into isoleucine in the presence of aminobutyric acid racemase[218].
10. Lactic acid derived bacteria (*e.g. Lactobacillus brevis* and *casei*) produce aspartic acid racemase[215]. The racemase can also be isolated from *Streptococcus thermophilus* or *lactis*; cysteic acid and derivatives can also be used as substrates[290].
11. Proline racemase is isolated from *Clostridium sticklandii* and is a remarkably stable enzyme[291]. Besides proline only hydroxyprolines are known as suitable substrates. A related racemase is isolated from *Flectbacillus* with a good specificity for 5-oxo-proline and 2-oxothiazole-4-carboxylate[292].
12. Glutamic acid racemase is a rather unstable enzyme mainly isolated from lactic acid bacteria[293]. The enzyme is applied in a process to convert inexpensive available L-glutamic acid into the D-enantiomer[293]. Other substrates are hardly accepted by glutamic acid racemase.

13. Two serine racemases are isolated from *Streptomyces garaphylus* a bacterium of importance for the production of the antibiotic D-cycloserine[294]. Japanese patents disclose various bacteria racemizing serine[295].

Table 19. Relative Activity of N-Acylamino Acid Racemase for Various Substrates[296].

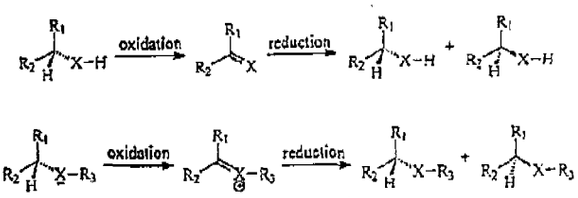
Substrate	Relative Activity (%)	Substrate	Relative Activity (%)
N-Acetyl-D-methionine	100	N-Acetyl-L-methionine	132
N-Acetyl-D-alanine	33	N-Acetyl-L-alanine	28
N-Acetyl-D-leucine	37	N-Acetyl-L-leucine	98
N-Acetyl-D-phenylalanine	64	N-Acetyl-L-phenylalanine	111
N-Acetyl-D-tryptophane	10	N-Acetyl-L-tryptophane	11
N-Acetyl-D-valine	80	N-Acetyl-L-valine	25
N-Formyl-D-Methionine	40	N-Formyl-L-Methionine	83
N-Chloroacetyl-D-phenylalanine	90	N-Chloroacetyl-L-phenylalanine	143
N-Chloroacetyl-D-valine	80	N-Chloroacetyl-L-valine	139
D-Methionine	0	L-Methionine	0
D-Alanine	0	L-Alanine	0
D-Leucine	0	L-Leucine	0
D-Phenylalanine	0	L-Phenylalanine	0
D-Tryptophane	0	L-Tryptophane	0
D-Valine	0	L-Valine	0

14. Isolated from various species, enzymes have been found that racemize α-phenyl-α-amino-acetonitrile, a phenylglycine precursor at low temperatures (3°C) in aqueous buffers[297]. A complete inversion of amino acids was performed by a coupled system of a D-amino acid oxidase and amino transferase[298]. L-Carnitine **80** was prepared from DL-carnitine by racemization with D-carnitine metabolizing microorganisms (*Actinobacter calcoaceticus*)[299]. The yield (37%) of isolated optically pure L-carnitine does not point to a dynamic kinetic resolution. (R)-Naproxen (R)-**33a** was racemized by a microorganism which may be a fungus (*e.g. Exophiala wilhansii*) or a bacterium (*e.g. Rhodococcus*), and whole cells or enzymes extracted from these cells. A kinetic resolution to optically pure enantiomers was observed for racemic naproxen **33a**, racemic ibuprofen **34** and racemic phenylglycine **41b** using *Exophiala wilhansii*[300]. Also a complete inversion of (R)-33a to (S)-33a was performed using an inverting enzyme system (fungus or bacterium)[301].

4.6 Racemization via redox and radical reactions.

Oxidations and reductions can be used to perform racemizations. Oxidation removes hydrogen from an asymmetric carbon, generating an intermediate species with a planar geometry. Reduction or hydrogenation restores the original hybridization state in a non-stereoselective way, thus generating a racemate (scheme 33). Racemization via hydrogen abstraction can also be realized by radical reactions. The oxidation and reduction can be performed simultaneously in a single step or in two separate steps (with or without isolation of the oxidized intermediate). Oxidative removal of groups other than hydrogen can also be used in racemization protocols. Racemization of amines can be performed under reductive conditions. Finally, redox reactions can

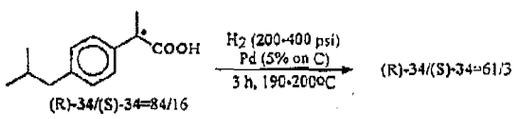
be used to epimerize compounds with two adjacent chiral centers. The respective possibilities are described below.



Scheme 33. Racemization via redox reactions.

4.6.1 Single-step processes.

The most efficient process is obtained when an equilibrium exists between the oxidized and reduced forms of the substrate. In many reactions using catalytic hydrogenation such an equilibrium exists, as the catalysts lowers the transition state. These methods are especially suitable when the asymmetric carbon in the substrate is activated by aryl groups. Ibuprofen **34** racemizes slowly at 190-200°C under hydrogen atmosphere in the presence of palladium or carbon catalyst (scheme 34)[101].



Scheme 34. Redox racemization of ibuprofen.

Other examples of these single-step racemizations involves amines. table 20 contains examples of benzylic amines and derivatives. The high yields indicate that in the case of amines hydrogenolysis of the heteroatom at the benzylic carbon atom plays no significant role. Activation of an asymmetric center by aryl groups however is not a '*conditio sine qua non*'. In Table 21 some substrates are collected lacking activation, which still undergo racemization.

Racemization of optically active secondary amines 131 (figure 15) was performed by Sumitomo workers under mild conditions by treatment of the amines with a catalyst which was obtained by coating a carrier (*e.g.* alumina, silica, charcoal) with an alkali metal (alloy) or by dispersing or dissolving an alkali metal in suitable media[103]. An example is the racemization of (R)-α-(1-naphthyl)ethylamine 82[104].

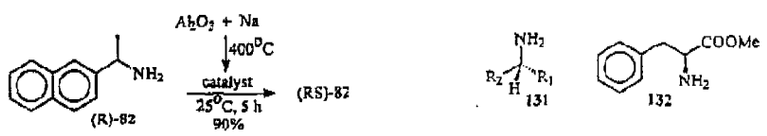
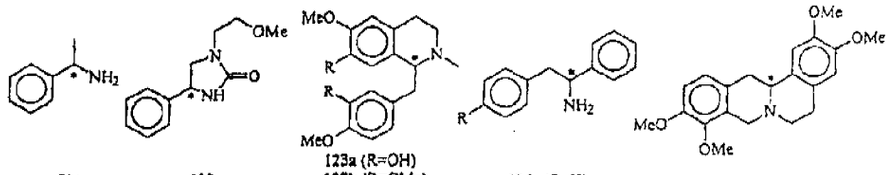


Figure 15. Reductive racemization of secondary amines.

Table 20. Single-step redox racemization of benzylic amines and derivatives.

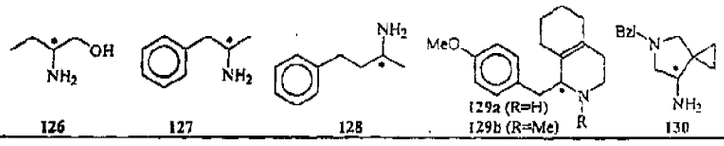


81a 122 123a (R=OH) 123b (R=OMe) 124a (R=H) 125

Entry	Substrate	Reaction Conditions	Yield (%)[a]	Racemization (%)[a]	Ref
1	**122**	Pd/C, 20-50 psig N_2, 24 h, 150°C, xylene	n.r.	100	305
2	**81**	H_2 (1 atm), Raney-Co, 15 h, 130°C	78.4	100	306
3	**123a**	H_2 (0.35 atm), PtO_2, HCl, EtOH	n.r.	n.r.	307
4	**123b**	H_2 (0.35 atm), PtO_2, 48 h, RT	81.3	100	308
5	**124a**	Raney-Ni, N_2, 1 h, 145-150°C	93	100	309
6	**125**	H2 (1 atm), PtO, AcOH, RT	91	100	310

a) n.r. = not reported.

Table 21. Single-step redox racemization of unactivated amines and derivatives.



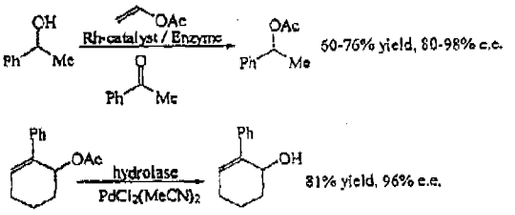
126 127 128 129a (R=H) 129b (R=Me) 130

Entry	Substrate	Reaction Conditions	Yield (%)[a]	Racemization (%)[a]	Ref
1	**126**	Rh/Al_2O_3, NH_3-gas, 60 h, 40°C	n.r.	42.5	311
2	**126**	H_2 (250 psi), Raney-Co, 7 h, 140°C	96	100	312
3	**126**	H_2/NH_3, 120-250°C, Pt, Pd, Co, Cu or Ni	n.r.	n.r.	313
4	**127**	H_2 (50 bar), Raney-Co, THF, 12 h, 160°C	95	98	314
5	**128**	H_2 (7.5 atm), Raney-Ni, 21 h, 150°C	76	97	315
6	**128**	H_2 (10-500 bar), Raney-Ni, no solvent, 50-300°C	n.r.	n.r.	316
7	**129**	H_2, prehydrogenated Pd/C, MeOH, 20°C	100	100	317
8	**130**	H_2 (100 atm), Raney-Co, THF, 24 h, 170°C	n.r.	100	318

a) n.r. = not reported.

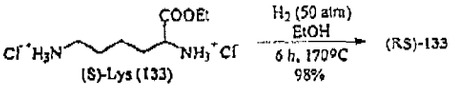
Alkali metal naphthalides have been used as catalyst in the racemization of secondary amine **124b** (*R=Me*)[319]. Reaction of optically pure **124b** with Na dispersed in naphthalene for 4 h at 25°C, yielded racemic **124b** in 85%. The method is also useful for the racemization of α-amino acid esters[320]; an example is the racemization of phenylalanine methyl ester **132** in 85% by treatment with Na/Al_2O_3 for 4 h at 25°C.

Metal catalyzed redox processes can also be employed in a dynamic kinetic resolution as was demonstrated by Williams and co-workers (Scheme 35)[321]. It was shown that enzymatic kinetic resolutions can be successfully combined with metal catalyzed racemizations.



Scheme 35. Metal catalyzed dynamic kinetic resolution

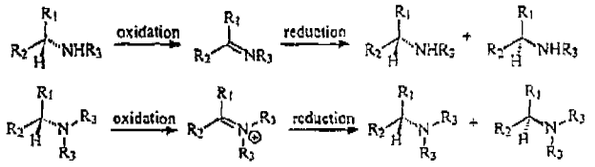
In this section should also be mentioned the somewhat surprising racemization of the ethyl ester of lysine bis-HCl salt **133** with hydrogen. No mention of a catalyst was made (scheme 36)[222].



Scheme 36. Racemization of ethyl lysinate.

4.6.2 Multi-step processes.

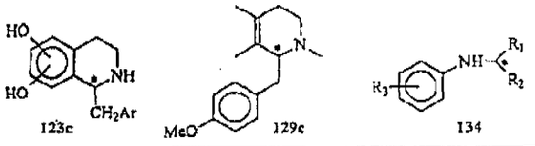
Racemization can also be achieved by performing the oxidation and the reduction in separate steps. This usually involves some form of chemical oxidation where no equilibrium exists. This approach has been applied to several optically active amines. In the first step a imine or immonium species is generated. Reduction in the second step leads back to the amine (scheme 37). Examples of this methodology are collected in table 22. In several instances the intermediate was not isolated.



Scheme 37. Multi-step redox racemization of optically active amines.

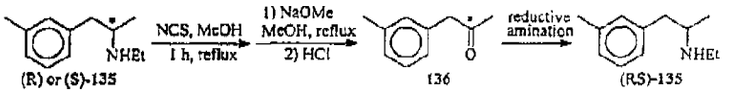
It can be advantageous to transform the undesired enantiomer, obtained by resolution, into an intermediate en route to the racemic mixture. For example, the unwanted enantiomer of 1-phenyl-2-aminopropane **135** can be oxidized to ketone **136**. Reductive amination of **136** leads back to racemic **135** (scheme 38)[223]. Oxidation, followed by reduction is an attractive strategy for racemization of other classes of optically active compounds as well, *e.g.* for alcohols.

Table 22. Multi-step Redox Racemization of Optically Active Amines.



Entry	Substrate	Reaction Conditions Oxidation	Reduction	Yield (%)[a]	Racemization (%)	Ref
1	**123c**	1) acylation. 2) $ArCH_2X$. 3) hydrolysis. 4) halogenation. 5) dehydrohalogenation	H_2, catalyst	n.r.	100	324
2	**129a**	1) NaOCl, MeOH, 0°C. 2) KOH	H_2, Raney-Ni, MeOH, RT	65	100	325
3	**129b**	NBS	$NaBH_4$, MeOH, 3 h, RT	97	100	326
4	**129b**	$Hg(OAc)_2$, Na_2(EDTA), AcOH	$NaBH_4$	82	100	327
5	**129c**	$Hg(OAc)_2$, AcOH/H_2O, 100°C	$NaBH_4$, EtOH, reflux	100	88	328
6	**134**	1) NaOCl. 2) NaOMe/MeOH	H_2, Pd/C	n.r.	100	329

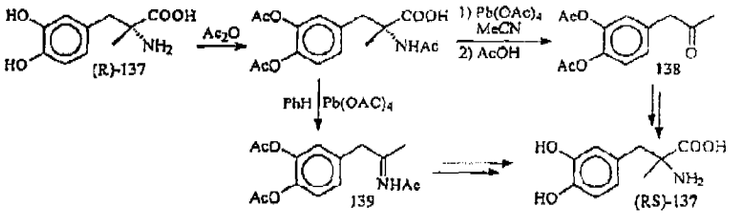
a) n.r. = not reported.



Scheme 38. Multi-step redox racemization of a 1-phenyl-2-aminopropane.

4.6.3 Racemization via oxidative degradation.

α-Me-Dopamine **137** does not contain a hydrogen at the asymmetric center. Reuse of the unwanted isomer from resolution processes is possible by oxidative decarboxylation to ketone **138** or amide **139**. This is another example of transforming an undesired enantiomer from a resolution process to an intermediate in the synthesis of the racemate (scheme 39)[330].



Scheme 39. Racemization via oxidative decarboxylation of α-Me-DOPA.

4.6.4 Racemization of two stereocenters.

Oxidation can be used as a method for racemization of components with two adjacent centers of chirality. Suitable candidates are, for example, optically active α-amino-alcohols **140**. Oxidation destroys chirality of one stereocenter, creating a carbonyl function. Racemization of the second stereocenter now can occur under enolization conditions as described in previous sections. The resulting racemate then has to be reduced (diastereoselectively) to the original compound as a racemate. It is evident that with a

diastereoselective reduction at hand this is a useful strategy for conversion of one diastereomer into racemic mixtures of the other diastereomer.

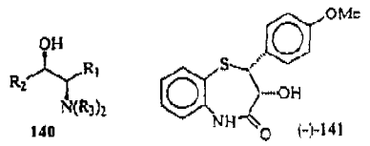
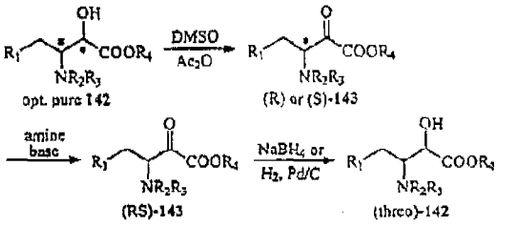


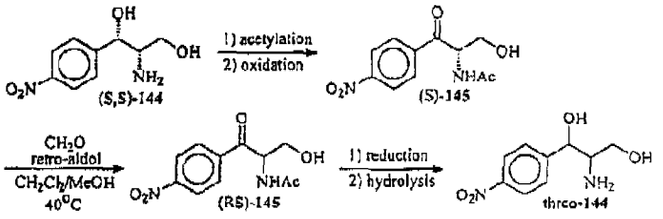
Figure 16.

An example of this methodology is the racemization of optically pure diltiazem precursor (-)-141 by oxidation with benzophenone and enolization by KOtBu at reflux. After stereoselective reduction with $NaBH_4$, racemic threo **141** is obtained in 70% yield[331].



Scheme 40. Racemization of two stereocenters of α-hydroxy-β-amino acid ester.

A second example is the racemization of α-hydroxy-β-amino acid esters **142** (scheme 40)[332]. A final example entails the unwanted isomer of chloramphenicol precursor **144** from a resolution process (scheme 41)[333]. After acetylation and oxidation to (S)-**145**, racemization of (S)-**145** takes place by a aldol/retro-aldol mechanism. Stereoselective reduction and hydrolysis leads to threo-**144**.



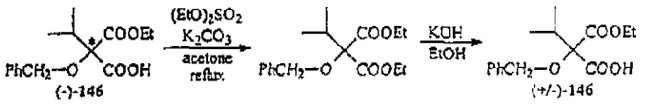
Scheme 41. Racemization of two stereocenters in a chloramphenicol precursor.

4.7 Miscellaneous racemization methods.

4.7.1 Racemization without reaction at the asymmetric center.

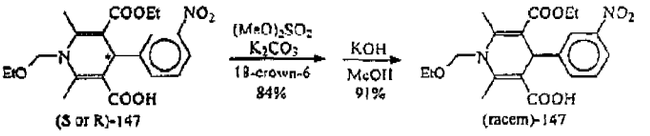
Most of the racemization procedures are characterized by disconnection and reconnection or substitution of one of the groups directly bound to the center of chirality. However, racemization techniques have been described in which the bonds in the asymmetric center are not involved. This can be accomplished

by rotation about bonds (c.f. section 4.1) or by making two of the functionalities at the stereocenter equal to give an achiral (meso) compound. After restoring the two original functionalities in a non-stereoselective way, a racemate is generated.



Scheme 42. Racemization of a malonic half-ester.

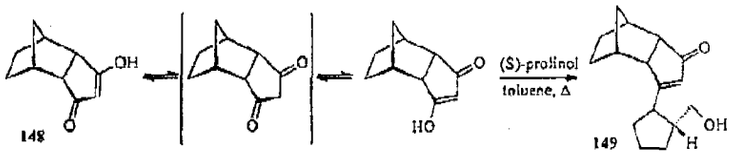
Malonic acid half-ester (-)-146, an unwanted isomer in a resolution process, is racemized by esterification to an achiral di-ester and subsequent hydrolysis to the racemic half-ester in an overall yield of 23% (scheme 42)[234]. A similar scenario has been optimized for the racemization of dihydropyridinecarboxylic acid 147 (scheme 43)[235].



Scheme 43. Racemization by esterification of a dihydropyridine dicarboxylic acid.

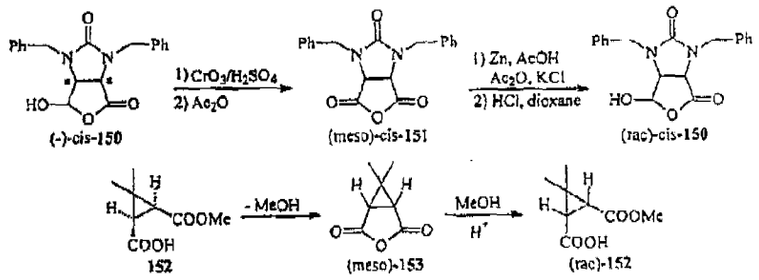
It is clear from these examples that the value of this approach depends on the preferred resolution route for preparation of optically active compounds like 146 and 147. As soon as methods are available for enantioselective mono hydrolysis of the achiral diesters these will be far more attractive than the combination of resolution of a racemate and racemization of the unwanted isomer.

Some meso- and prochiral diesters are also suitable substrates in enzyme catalyzed enantioselective hydrolysis to optically pure half-ester in yields up to 100% (meso trick)[216]. Dynamic kinetic resolution of pseudo-meso 5-hydroxytricyclodecadienone 148 using (S)-prolinol leads to the corresponding enaminones 149 in a yield of 91% and with a de of 50% (scheme 44)[227].



Scheme 44. Dynamic kinetic resolution of 5-hydroxytricyclodecadienone.

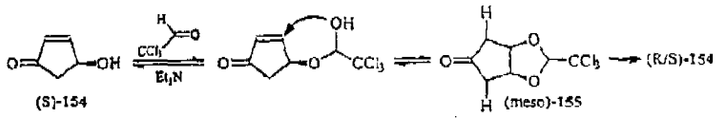
Two more examples of this type of racemization are shown in scheme 45. Compound 150 is racemized via oxidation to meso-compound 151 and final reduction to racemic 150[236]. Cyclopropane half-ester 152 is racemized via meso-compound 153[237] (see also section 4.3, scheme 20).



Scheme 45. Racemization via meso-compounds.

4.7.2 Transfer of the center of chirality.

4-Hydroxy-2-cyclopentenone **154** was racemized by treatment with chloral and a tertiary amine as catalyst in 5 hours at 10°C (scheme 46)[140]. It is tentatively supposed that this reaction proceeds via acetalization of **154** with chloral and subsequent ring-closure to meso-compound **155**. Enol formation induced by the basic catalyst yields both enantiomers of **154** (see also section 4.3 Scheme 20, racemization of compound **97**).



Scheme 46. Racemization of 4-hydroxy-2-cyclopentenone.

4.7.3 Racemization of α-aminocarbonitriles and cyanohydrins.

α-Aminocarbonitriles **156** and related compounds are intermediates in the manufacture of α-amino carboxylic acids via Strecker-type reactions starting with aldehydes or ketones (figure 17). Compounds **156** can be resolved with chiral acids and the unwanted isomer can be racemized with cyanide ions[141]. For example, D-α-aminophenylacetonitrile **157** was racemized by treatment with KCN in MeOH at 40°C for 10 min.

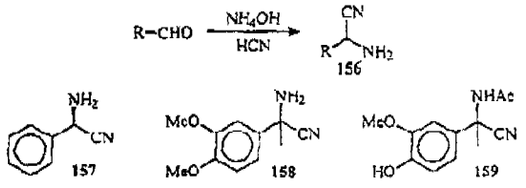
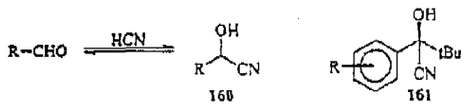


Figure 17. α-Aminocarbonitrils

For Strecker adducts from ketones, racemization at this stage in the synthesis of the corresponding α-amino acids is of special importance. Racemization via deprotonation-protonation is not possible for these compounds. A rather complicated solution to this problem was shown in section 4.6.3 for α-methyl dopamine

(scheme 39). The D-enantiomer of 2-amino-2-(3,4-dimethoxybenzyl)propionitrile **158** was racemized as its (-)-dibenzoyl-tartrate salt in 12N ammonia for 30 min at 50°C in 45% yield[342]. Compound **159** was racemized by NaCN in refluxing DMSO[343]. The reaction proceeds via deprotonation of the amide function, followed by rate-determining expulsion of cyanide ion[344], thus showing show strong resemblance with the racemization of α-aminonitriles.

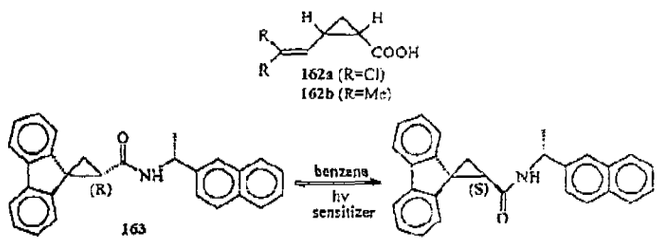


Scheme 47. Synthesis and racemization of cyanohydrins.

Cyanohydrins **160** are receptive for racemization because they can be equilibrated with the corresponding aldehyde/ketone and HCN (scheme 47). In the crystallization-induced asymmetric transformation of cyanohydrin **161** this equilibrium is combined with brucine complexation and crystallization of one diastereomeric complex. Depending on the phenyl substituent, brucine-cyanohydrin complexes are isolated in 40-100% yield and with ee's of 50-100%[345]. This equilibrium of cyanohydrins is also applied in dynamic kinetic resolutions using lipases to prepare cyanohydrin acetates[346].

4.7.4 Photochemical racemizations.

Irradiation with UV-light in the presence of a sensitizer has been used during the racemization of dichlorovinylcyclopropylcarboxylic acids **162a**[347] and **162b**[348], which contain two centers of chirality (scheme 48). Ring-opening and closure during irradiation leads to annihilation of chirality at both centers, but ring-closure leads to a mixture of both cis- and trans-racemate. To separate the diastereomers the mixture was treated with $BF_3.Et_2O$. The cis-compound gives a lactone and the trans-compound remains unaffected. Cis- and trans-racemates can then be separated by simple base extraction.

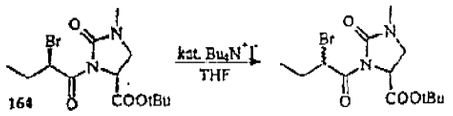


Scheme 48. Photochemical racemization.

A photo-induced first-order asymmetric transformation of cyclopropane derivative **163** was observed (scheme 48). From optically pure 2'-(R)-**163** or 2'-(S)-**163** the same R/S ratios are obtained. The isomerization follows a ring-opening mechanism and is initiated by radicals. Different diastereomeric ratios are obtained depending on the triplet-energy of the sensitizer and therefore, the energy transfer from the sensitizer to **163** is probably the key step for the isomerization[349].

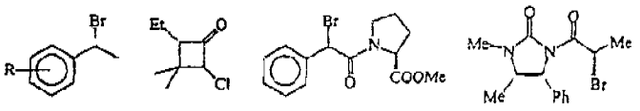
4.7.5 Racemization via substitution of halogen ions

α-Bromocarboxylic acid derivatives can be racemized by nucleophilic substitution of the bromine by halide ions. This concept was shown in the epimerization of compound **164** by tetrabutylammonium iodide (scheme 49). This racemization procedure was applied in the dynamic kinetic resolution of several other α-halo acid derivatives in which the bromine is substituted by an amine resulting in optically pure amino acid derivatives[350]. In a similar procedure optically pure α-aryloxy and α-hydroxycarboxylic acids were prepared by a dynamic kinetic resolution of α-halocarboxylic esters. In this case a stereoselective nucleophilic substitution with alkoxides is combined with an in situ epimerization induced by *n*-hexylammonium iodide[351].



Scheme 49. Racemization of an α-bromoamide by nucleophilic substitution.

The racemization of 1-bromo-1-arylethanes **165** and 2-bromooctane was studied by bromide exchange[352]. A racemization at two stereocenters was observed for cyclobutanones **166**. Racemization of the (-)-cis-**166** takes place by enolization and a double cine-rearrangement induced by tetrabutylammonium chloride at 120°C or by HBr in AcOH at 25°C[353]. Racemization via a reversible substitution mechanism of bromide is probably the cause for the crystallization-induced asymmetric transformation of **167**, because in hydrogen-deuterium exchange experiments in CD_3OD no deuteration of **167** could be observed. Compound **167** was isolated with 0-100% ee in almost quantitative yields[354]. Another example of crystallization induced asymmetric transformation is shown by compound **168**. The 2'-R/S mixture epimerizes under the influence of Bu_4NBr. Slow evaporation of the solvent leaves **168** with a d.e. >98%[355]



165 **166** **167** **168**

Figure 18.

5. CONCLUSIONS.

This review clearly demonstrates the lack of systematics in the research on racemizations. The strong emphasis on carboxylic acids and derivatives (75% of all our examples, of which 60% pertain to aminoacids) is remarkable. The industrial relevance of this type of compounds, both as building blocks and end products, is a realistic explanation for this preference. We made a classification of several racemization methods subdivided by some classes of compounds which may be helpful to develop new racemization reactions.

The current industrial and social awareness of unambiguous chirality in pharmaceuticals will certainly keep the subject actual. As in the past, this will mostly be the avoidance of racemization in the design of syntheses for chiral products. This will particularly be true in asymmetric synthesis. The more so because industrially relevant synthesis of optically active products increasingly have to meet the demand of 100% yield and 100% ee. For resolution processes to meet this criterion an efficient racemization step is

indispensable. Combination of classical resolution processes with *in situ* racemization to give asymmetric transformations will be necessary to keep up with the advances in asymmetric synthesis. This will be equally true for resolutions using biocatalysts (*e.g.* dynamic kinetic resolutions). In these processes there will be a growing need for mild racemization conditions and simple work-up procedures. The use of racemases and solid supports is expected to gain considerable interest. Recent work in our group shows promising results in the immobilization of strong bases as part of an asymmetric transformation process[356].

6. REFERENCES

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Biographical Sketch

Eelco J. Ebbers

Gerry J. A. Ariaans

Joannes P. M. Houbiers

Alle Bruggink

Binne Zwanenburg

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Eelco J. Ebbers received his MSc degree in 1992 and his PhD in 1997 from the University of Nijmegen under the supervision of Profs. Bruggink and Zwanenburg. For his PhD degree he studied the racemization and asymmetric transformation of α-substituted carboxylic acids.

Gerry J.A. Ariaans received his MSc degree in 1982 and his PhD in 1987 from the University of Nijmegen under the direction of Professor B. Zwanenburg. After a short period in industry he joined the group of Profs. Bruggink and Zwanenburg at the University of Nijmegen in 1989, studying methods for the optimization of classical resolution procedures and methods for quantifying chirality. Since 1991 he is also involved in a cooperation project with the University of Dar es Salaam (Tanzania).

Joannes P.M. Houbiers studied chemistry and prepared his PhD thesis on the stereochemistry of spiranes, under the guidance of Prof. H. Wijnberg at the University of Groningen. In 1969 he joined the Research department of Océ-Andeno (from 1987 : DSM-Andeno) in Venlo, The Netherlands. In 1994 he retired from industry and since 1995 works part-time at the University of Nijmegen, The Netherlands.

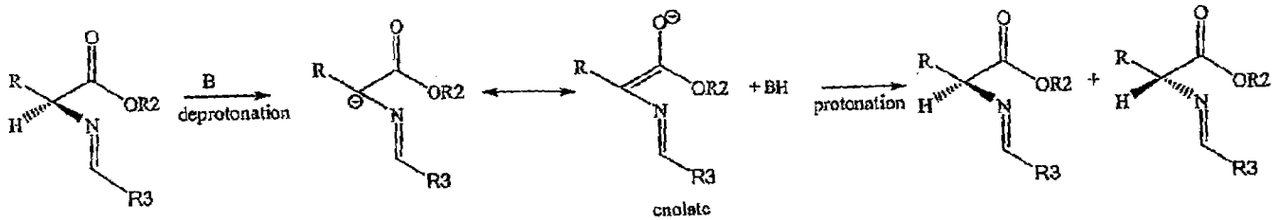
Alle Bruggink was born in Fochteloo, (the northern part of) The Netherlands. In 1971 he received his PhD degree from the University of Groningen (The Netherlands) on physical organic chemistry (with prof. J. Strating). He did postdoctoral work with prof. Hogeveen at the University of Groningen from 1971-1972 and at the University of East Anglia in Norwich, United Kingdom with prof. McKillop.
In 1974 he accepted a position as research manager at Océ-Andeno in Venlo, The Netherlands and in 1986 he became Manager Strategy and Marketing-Research at DSM-Andeno in Venlo. From 1991-1994 he was R&D Director at the same company. In 1988-present he was appointed part-time Professor Industrial Organic Chemistry at the University of Nijmegen, The Netherlands. His present position as Director Technology & Strategy at Chemferm in Breda, The Netherlands was accepted in 1994.
His current research interests are chirality, biocatalysis, international development of fine chemical industry, fine chemicals and pharmaceuticals and sustainable technology development.

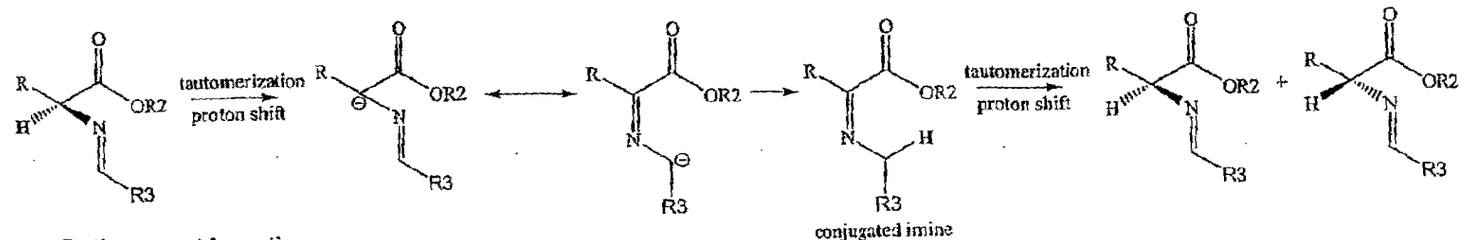
Binne Zwanenburg was born in Lippenhuizen, (the northern part of) The Netherlands. He received his MSc and Doctor's degrees from the University of Groningen (The Netherlands) in 1959 and 1962, respectively, on a kinetic study of acetylenic ethers under the supervision of Profs. J.F. Arens and W. Drenth. He did postdoctoral work with Prof. R.A. Raphael, at the University of Glasgow (Scotland) on the Favorskii rearrangement (1963) and with Prof. N.J. Leonard at the University of Illinois (Urbana-Champaign, IL) on azirine chemistry (1964-1965). He joined the research group of Prof. J. Strating in 1961 and studied the synthesis of sulfines and the mechanism of reaction of diazo sulfones. He was appointed Assistant Professor at the University of Groningen in 1963 and Associate Professor in 1965. He accepted his present position as Professor of Organic Chemistry at the University of Nijmegen in 1971. His current research interests are organic sulfur chemistry, functionalized epoxides, strained polycyclic systems, design and synthesis of germination stimulants, organic enzyme chemistry, flash-vacuum-thermolysis, asymmetric synthesis, natural product synthesis, and the utilization of clay minerals as catalysts in organic synthesis.
Binne Zwanenburg has served on many Boards and Committees, both national and international, during his career. Among these are Chairman of the Netherlands Foundation for Chemical Research (SON) (1985-1991), member of the Advisory Board International Symposia on Organosulfur Chemistry (1986- present), Chairman of NATO-panel Advanced Study Institutes/Advanced Research Workshops (1994), Chairman of the National Foresight Committee of Chemistry (1993-1996).

Attachment 3:

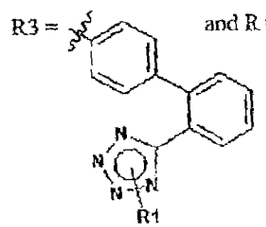
Re: European Patent No.: 1546122 (European Application No.: 03750599.7)

Racemization of chiral imines formed during a reductive amination step, under basic conditions, with an amino acid





In the present invention:

R3 =  and R = isopropyl, B = base

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES
RESPUESTA AL RECURSO DE REPOSICIÓN

Radicación 05 27433
Clasificación Internacional (CIP) C07D 257/04

Patente de Invención	[x]	Patente de Modelo de Utilidad		[ ]
Vía Nacional	[ ]			
Vía PCT (Fase Nacional)	[x]	Cap. I	[ ]	Cap. II [x]

No. Solicitud Internacional PCT/EP2003/010543
Fecha de Presentación Internacional 22/Septiembre/2003

Título inicial: "Proceso para la fabricación de valsartán".

En atención al Recurso de Reposición interpuesto en contra de la resolución No. 23612 de fecha 30 de Abril de 2010, se presenta el siguiente concepto:

1. Documentos estudiados

Para el presente estudio se consideraron el capítulo descriptivo comprendido en los folios 6 – 63, el nuevo capítulo reivindicatorio de los folios 211-217 y las observaciones formuladas por el señor recurrente en el recurso de reposición de los folios 256 - 262 de la solicitud en estudio.

La presente solicitud reivindica el derecho de prioridad sobre las siguientes solicitudes: GB 0222056.4 de 23 de Septiembre de 2002

2. Objeto de la Invención

El problema planteado en esta solicitud consiste en la necesidad de desarrollar variantes del proceso para la fabricación de valsartán que excluyan el uso de azidas en los últimos pasos de la producción en menos pasos de reacción y con producto final enantioméricamente puros

Para resolver este problema técnico la solicitud en estudio proporciona un proceso de síntesis de valsartán que comprende: a) una aminación reductiva del compuesto IIa, b) acilar el compuesto resultante, c) remover los grupos protectores y d) aislar el compuesto resultante

3. Respuesta a los Argumentos del señor recurrente

En atención a los argumentos del señor recurrente se hacen las siguientes

aclaraciones:

3.1 Argumentos respecto a D1:

3.1.1 El señor recurrente sostiene que: *"...la misma presenta dos variaciones en la síntesis de valsartán...La diferencia técnica entre la preparación de valsartán de acuerdo con la primera variante y...la presente invención es el uso de un proceso de aminación reductiva bajo condiciones ácidas...para proporcionar sin racemización una amina quiral de fórmula (IIC)...D1 no menciona ningún proceso de aminación reductiva bajo condiciones básicas...el técnico con habilidad ordinaria...no podria verse motivado a efectuar una aminación reductiva con un aminoácido quiral en condiciones básicas...D1 solo muestra la presencia del enantiómero deseado al final de la reacción, después de la purificación...nada puede decirse respecto a la racemización en medio básico, ya que las rutas mecánicas para las racemización no son las mismas a diferente pH...bajo condiciones ácidas...involucraría enoles...las tasas cinéticas...no serían las mismas a pH ácido que a pH básico...Por lo tanto, en vista de D1...la elección de llevar a cabo la aminación reductiva en condiciones ácidas con un aminoácido quiral no es directa...Es así como la falta de racemización...bajo condiciones básicas ...es sorprendente...por sobre D1...En una segunda variante...la diferencia técnica...y la preparación de valsartán de acuerdo con la presente solicitud es el uso de la aminación reductiva en condiciones básicas...para proporcionar, sin racemización, una amina secundaria de fórmula (IIC)...partiendo de la segunda variante de D1, el problema técnico objetivo...es proporcionar un método nuevo y económicamente atractivo para preparar una amina secundaria quiral intermedia para la preparación de valsartán...el técnico con habilidad en la materia no se vería motivado a intentar la aminación reductiva empleando un aminoácido quiral bajo condiciones básicas..."*

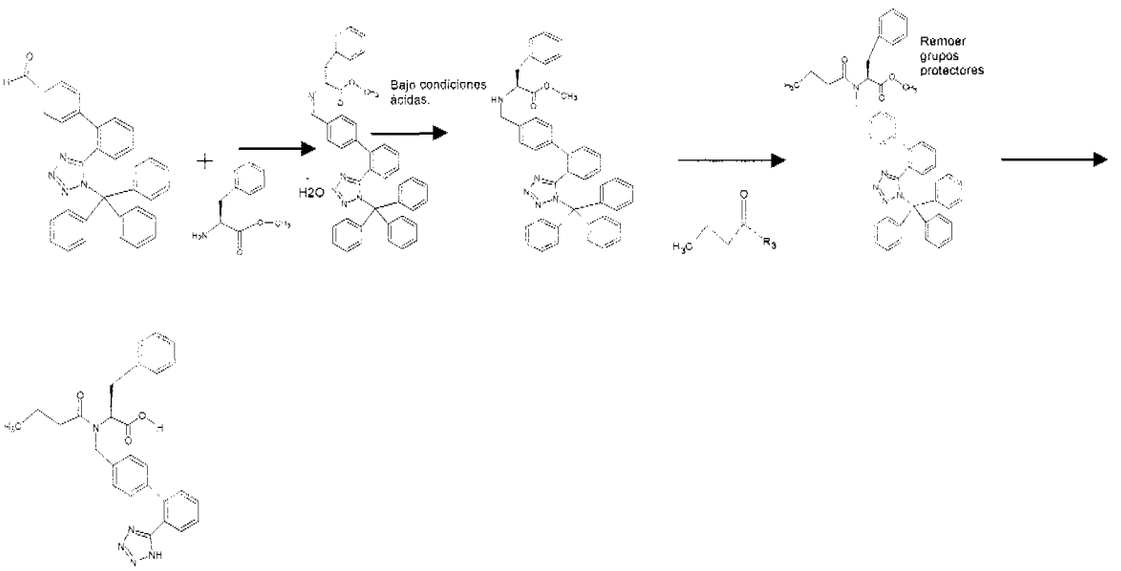
Se aclara al señor recurrente que parece que se hace referencia a US 5399578, el cual no fue relacionado dentro del concepto técnico de negación, por lo tanto, dicho argumento no es relevante dentro de la discusión de falta de nivel inventivo, ya que en el oficio 16158 de 19 de Diciembre de 2008, en su estudio de la oposición, se dijo que dicho documento no es relevante para el estudio de patentabilidad. En conclusión, los argumentos que presenta el solicitante con respecto a US 5399578 no serán estudiados, ya que dicho documento no se relacionó como relevante para afectar la patentabilidad de la solicitud.

3.2. Argumentos sobre D2

3.2.1. El recurrente afirma que *"...dicha anterioridad divulga un método para la fabricación de antagonistas de angiotensina II de fórmula I, los cuales no comprende al valsartán. De acuerdo con...(el) esquema 2a puede prepararse...bajo condiciones ácidas...la persona con habilidad en la materia no habría encontrado en D2 un indicio que lo llevara a realizar una aminación reductiva bajo condiciones básicas"*

Parece que el recurrente se refiere a US 5260325, que corresponde a D1 dentro de la resolución de negación y, si bien dicho documento no revela el compuesto valsartán, dicho documento es relevante, ya que revela un mecanismo de reacción muy similar al reivindicado partiendo del mismo

compuesto de partida (IIa de la presente solicitud, veamos:



(ejemplo 2, Columna 15 de D1), el cual se diferencia de la presente solicitud en que no se mencionan unas condiciones ácidas de la reacción, sin embargo D2 (Quimica organica. Ralph y Joan Fessenden. Grupo Editorial Iberoamericana. Sección 11.15. Oxidación de aldehídos y Cetonas.) enseña que la aminación reductiva puede realizarse en condiciones básicas (página 549), es decir, provee la diferencia y el efecto técnico que concede la presente solicitud, por lo tanto, una persona versada en la materia, estaría en condiciones de modificar el proceso enseñado en el ejemplo 2 de D1 y aplicar condiciones las condiciones básicas para la aminación reductiva de D2, con la expectativa de llegar al procedimiento alternativo de síntesis de valsartán que se reivindica. En conclusión es la combinación de enseñanzas de D1 con D2 la que afecta el nivel inventivo de la presente solicitud.

3.2. Argumentos sobre el nivel inventivo

3.2.1. El señor recurrente continúa diciendo que *"...aunque el examinador tiene razón en cuanto a las condiciones de pH y presencia de una fuente de protones capaz de garantizar la reacción, para el técnico con habilidad ordinaria...no es fácil derivar a partir de las condiciones de la aminación reductiva de D1,D2 o D3 un proceso que incorpore dicha etapa de aminación...sin que sea necesario implementar un proceso aparte. Esto, de por sí, es un efecto sorprendente de la presente invención..."*

Se le aclara al recurrente que, tal como se indicó en el punto anterior, la combinación de las enseñanzas del ejemplo 2 de D1 (columna 15) con las enseñanzas de D2, pagina 549, relacionadas con aminación reductiva en medio básico, llevarían a una persona versada en la materia al procedimiento de síntesis reivindicado con la expectativa de producir valsartán sin necesidad de implementar un proceso aparte, tal como ocurre con el procedimiento de la presente solicitud.

3.2.2. El recurrente asegura que *"(en) la presente solicitud todo el proceso se*

lleva a cabo bajo condiciones básicas, lo cual hace necesario incorporar otras condiciones...reactivos y otros grupos protectores que no se mencionan ni se sugieren en el estado de la técnica..."

Se le aclara al recurrente que, D1 ya enseñaba un procedimiento muy similar al reivindicado, partiendo del mismo compuesto de partida donde se obtienen compuestos muy parecidos al valsartán, en cuanto a los grupos protectores, D5 (folios 189-195) ya enseñaba el uso de diferentes grupos protectores sobre el grupo carbóxilico o sobre grupos amino en síntesis química, por lo tanto, una persona versada en la materia estaría en capacidad de tomar los grupos protectores de D5 para los intermediarios de la parte B del ejemplo 2 de D1 y, de esta manera, obtener los compuestos intermedios que se reivindican en las reivindicaciones 8 y dependientes de la presente solicitud.

3.2.3. El recurrente afirma que *"...El examinador parece enfocarse ...en las fórmulas de los intermedios y en el proceso de aminación reductiva, sin tener en cuenta las condiciones totales del proceso...sorprendentemente se ha encontrado que una amina quiral de fórmula (IIc)...puede prepararse mediante la reacción de aminación reductiva bajo condiciones básicas sin racemización. Tal amina es el producto de un paso de aminación reductiva...Es bien sabido...que los aminoácidos quirales pueden racemizarse bajo condiciones básicas...Para sustentar esto...(se) adjunta un artículo de Ebbers...en particular...las secciones 4.2 y 4.4 del mismo...se hace referencia al segundo párrafo de la página 9433 el cual enumera los factores que influencian y afectan la tasa de racemización..."*

Se le aclara al recurrente que de la lectura del artículo enviado como anexo al presente recurso, se observa que se refiere a la utilidad de la racemización como alternativa económica de las síntesis asimétricas. De otra parte, la sección 4.2 de dicho documento, efectivamente se relaciona con racemización en medio básico, pero enseña a página 9430 que se necesita la preparación de un derivado y que las bases usadas para tal fin incluyen hidróxidos, alcoholatos, amidas y aminas, enseñándose a tabla 4 (página 9432) que para llegar a una racemización de aminoácidos se requiere un pH mayor de 10, cloruro de litio y altas temperaturas, es decir, se necesitan condiciones muy específicas para que los aminoácidos se racemicen, confirmando lo dicho por este despacho en cuanto a las enseñanzas de D2 que enseña que la aminación reductiva se puede efectuar en condiciones básicas sin ningún problema en especial. En conclusión, las enseñanzas del artículo de Ebbers, no son relevantes para desvirtuar la falta de nivel inventivo de la presente solicitud.

3.2.4. El recurrente insiste en que *"...El proceso reclamado es económicamente ventajoso para la fabricación comercial de...valsartán...si la preparación sintética de una droga incluye un paso en donde hay racemización, se requieren pasos adicionales...Además...el rendimiento total de la ruta sintética disminuye a medida que se incrementan el número de pasos de síntesis...Ambos son...altamente deseables para los procesos de fabricación a una escala industrial...se resalta ...en el último párrafo de la página 9465 del anexo 1*

Cabe anotar que, tal como se ha ido explicando, el proceso de aminación reductiva puede ser efectuado sin complicaciones en medio básico, tal como

enseña D2 a página 549 y que se confirma con el anexo del solicitante que enseña que para que los aminoácidos sean racemizados se necesitan de condiciones muy específicas, es decir la combinación de las enseñanzas de D2 dentro del procedimiento del ejemplo 2 de D1 (columna 15) enseñan de manera evidente a llegar al procedimiento reivindicado con la expectativa de producir valsartán sin ninguna clase de racemización. Además ante la ausencia de datos que demuestren una ventaja técnica real (mayor rendimiento, etc.) frente a lo conocido en el estado de la técnica, no es posible reconocerle nivel inventivo al procedimiento reivindicado.

4. Conclusión

Teniendo en cuenta lo anterior, se recomienda confirmar la decisión consignada en la Resolución No. 23612 de 30 de Abril de 2010 donde se niega del privilegio solicitado para las reivindicaciones 1 – 11 (folios 211-217).

Elaboró: Andrés Gil
Revisado por: Consuelo Leguizamón