



(86) Date de dépôt PCT/PCT Filing Date: 2001/09/14

(87) Date publication PCT/PCT Publication Date: 2003/03/12

(85) Entrée phase nationale/National Entry: 2003/03/12

(86) N° demande PCT/PCT Application No.: EP 2001/010626

(87) N° publication PCT/PCT Publication No.: 2002/022569

(30) Priorité/Priority: 2000/09/14 (100 45 832.7) DE

(51) Cl.Int.⁷/Int.Cl.⁷ C07C 323/60, A61K 31/10, A61P 25/04

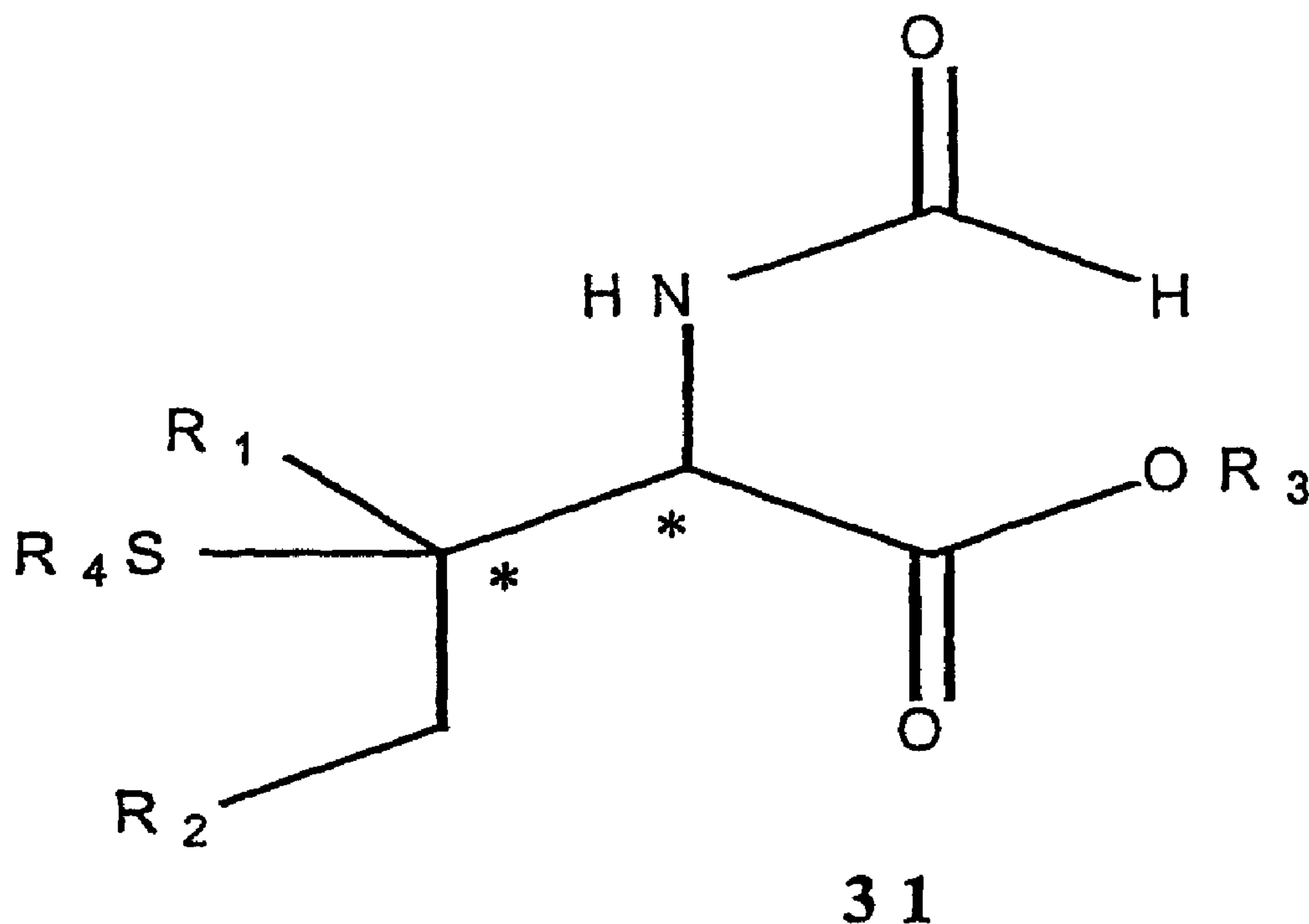
(71) Demandeur/Applicant:
GRUNENTHAL GMBH, DE

(72) Inventeurs/Inventors:
GERLACH, MATTHIAS, DE;
PUTZ, CLAUDIA, DE;
ENDERS, D., DE;
GAUBE, GERO, DE

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : PROCEDE POUR PRODUIRE DES COMPOSES CHIRAUX

(54) Title: PROCESS FOR THE PRODUCTION OF CHIRAL COMPOUNDS



(57) Abrégé/Abstract:

The invention relates to a method for producing chiral compounds according to the condition of a 1.4 Michael reaction in addition to a compound of general formula (31) and the use thereof as an analgic.



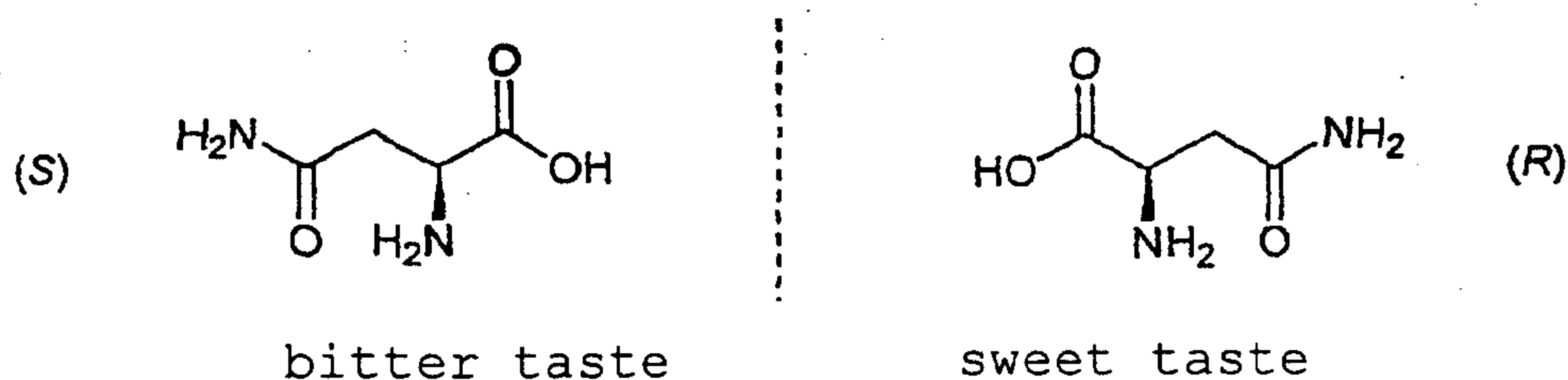
Process for the production of chiral compounds

The invention relates to a process for the production of
5 chiral compounds under 1,4-Michael addition conditions and
to corresponding compounds.

Asymmetric synthesis

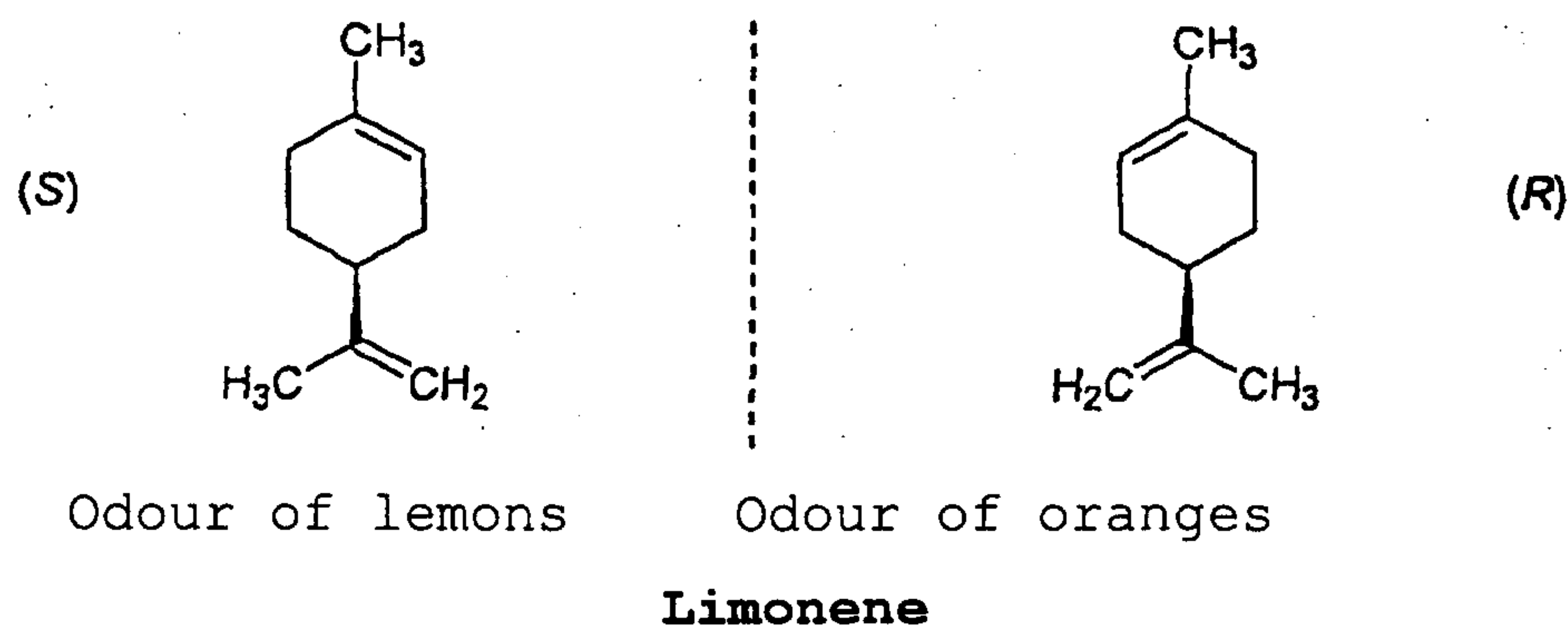
10 Asymmetric synthesis is the central theme of the present
application. A carbon atom may form four bonds which are
spatially oriented in a tetrahedral shape. If a carbon atom
bears four different substituents, there are two possible
arrangements which behave to one another as image and
15 mirror image. These are known as enantiomers. Chiral
molecules (derived from the Greek word cheir meaning hand)
have no axis of rotational symmetry. They merely differ in
one of their physical properties, namely the direction in
which they rotate linearly polarised light by an identical
20 amount. In achiral environments, the two enantiomers
exhibit the same chemical, biological and physical
properties. In contrast, in chiral environments, such as
for example the human body, their properties may be very
different.

25



Asparagine

30



5 **Figure 1:** Examples of enantiomers with different biological properties.

In such environments, the enantiomers each interact differently with receptors and enzymes, such that different physiological effects may occur in nature (see Figure 1)[1]. For example, the (S) form (S from Latin sinister = left) of asparagine has a bitter flavour, while the (R) form (R from Latin rectus = right) tastes sweet. Limonene, which occurs in citrus fruit, is one everyday example. The (S) form is reminiscent of lemons in odour, while the (R) form smells of oranges. In general, literature references are denoted in the description by Arabic numerals in square brackets which refer to the list of references located between the list of abbreviations and the claims. Where a Roman numeral appears after a literature reference, which is usually cited by the first author's name, the corresponding value (in Arabic numerals) is intended, as it is where the value is not enclosed between square brackets.

25 Enantiomerically pure substances may be produced by three different methods:

- conventional racemate resolution
- using natural chiral building blocks ("chiral pool")
- 30 • asymmetric synthesis.

Asymmetric synthesis in particular has now come to be of particular significance. It encompasses enzymatic, stoichiometric and also catalytic methods. Asymmetric catalysis is by far the most efficient method as it is possible to produce a maximum quantity of optically active substances using a minimum of chiral catalyst.

The discoveries made by Pasteur[2], LeBel[3] and van't Hoff[4] aroused interest in optically active substances, because their significance in the complex chemistry of life had been recognised.

D. Enders and W. Hoffmann[1] define asymmetric synthesis as follows:

15

"An asymmetric synthesis is a reaction in which a chiral grouping is produced from a prochiral grouping in such a manner that the stereoisomeric products (enantiomers or diastereomers) are obtained in unequal quantities."

20

If an asymmetric synthesis is to proceed successfully, diastereomorphic transition states with differing energies must be passed through during the reaction. These determine which enantiomer is formed in excess. Diastereomorphic transition states with different energies may be produced by additional chirality information. This may in turn be provided by chiral solvents, chirally modified reagents or chiral catalysts to form the diastereomorphic transition states.

30

Sharpless epoxidation is one example of asymmetric catalysis[5]. In this reaction, the chiral catalyst shown in Figure 2 is formed from the Lewis acid $\text{Ti}(\text{O}-i\text{-Pr})_4$ and (-)-diethyl tartrate.

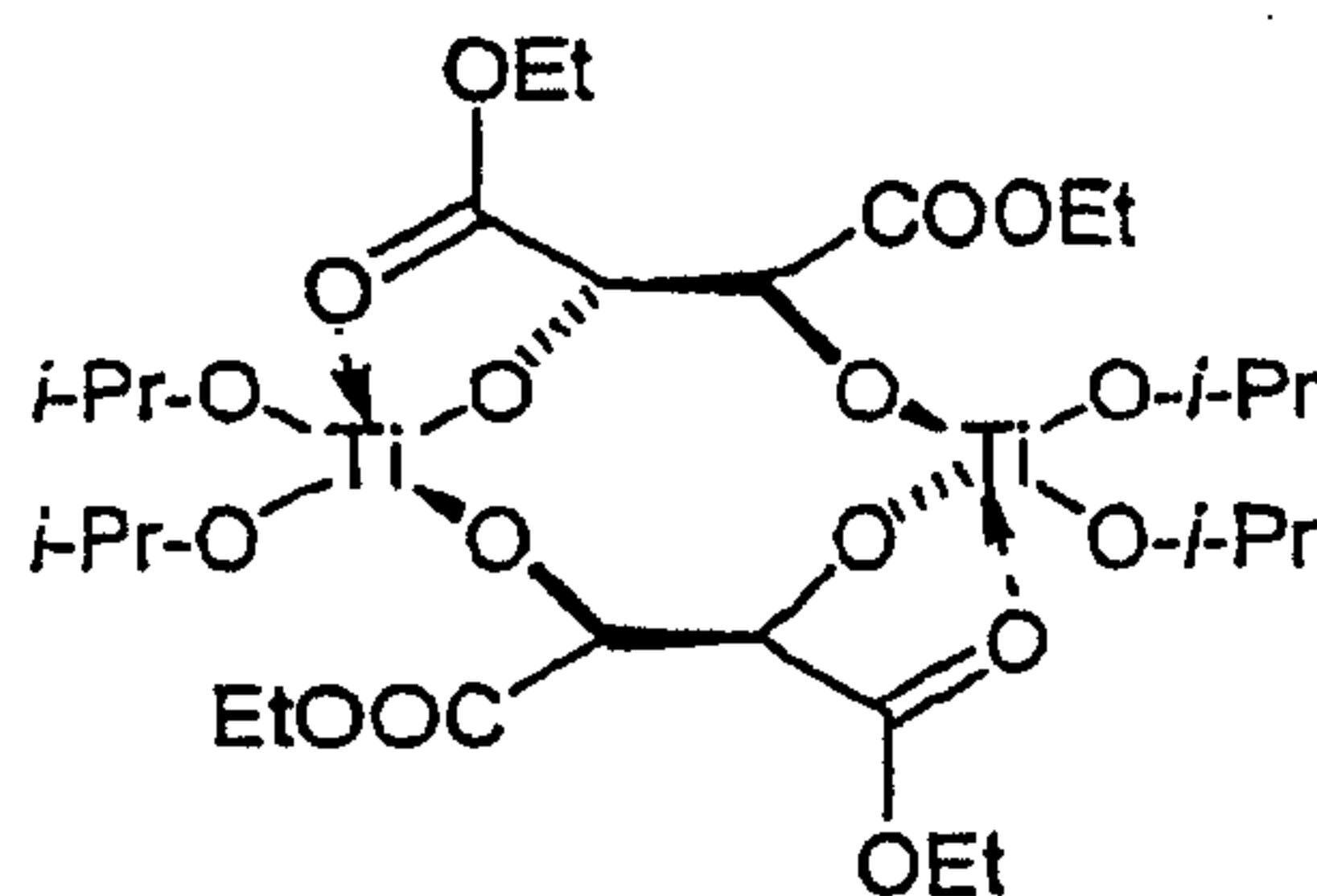


Figure 2: Chiral catalyst of Sharpless epoxidation[5].

Using this catalyst, allyl alcohols **1** may be epoxidised
 5 highly enantioselectively to yield **2** (see Figure 3),
 wherein tert.-butyl hydroperoxide is used as the oxidising
 agent.

In general, in the description those compounds, in
 10 particular those shown in a Figure or described as a
 general formula, are mainly, but not always, designated and
 marked with corresponding bold and underlined numerals.

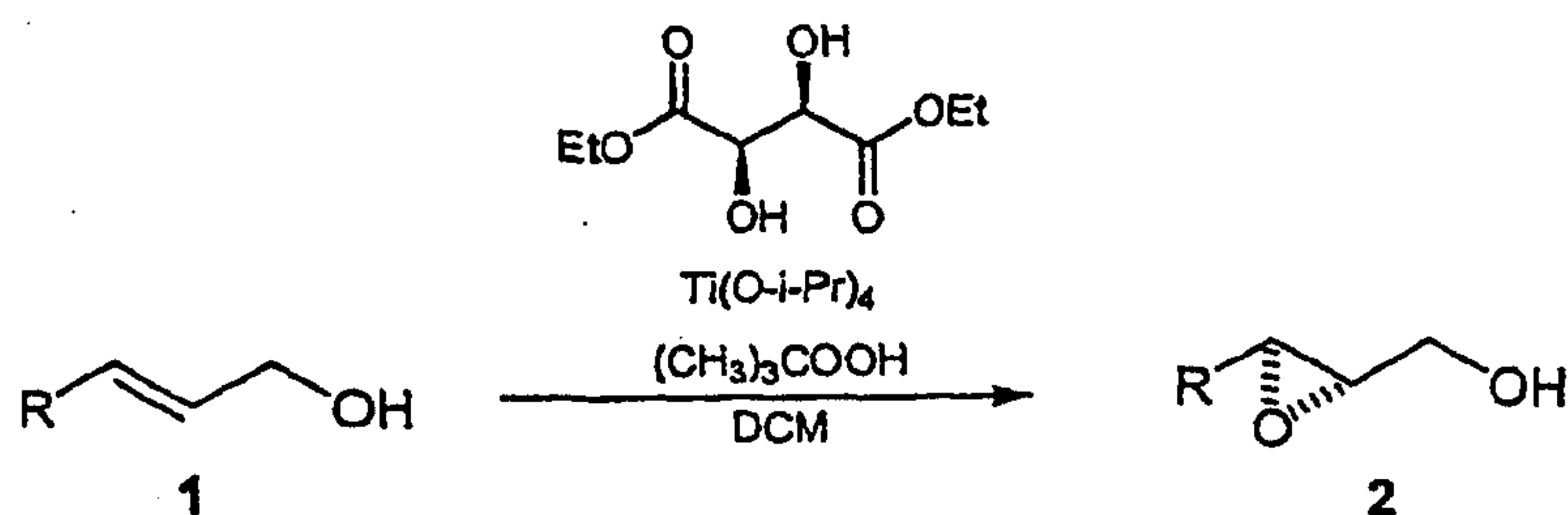


Figure 3: Sharpless epoxidation.

15

The Sharpless reaction is now a widely used reaction,
 especially in the chemistry of natural substances.
 Compounds such as alcohols, ethers or vicinal alcohols may
 readily be prepared at an optical purity of >90% by
 20 nucleophilic ring-opening.

The Michael reaction

The Michael reaction is of huge significance in organic
 25 synthesis and is one of the most important C-C linkage

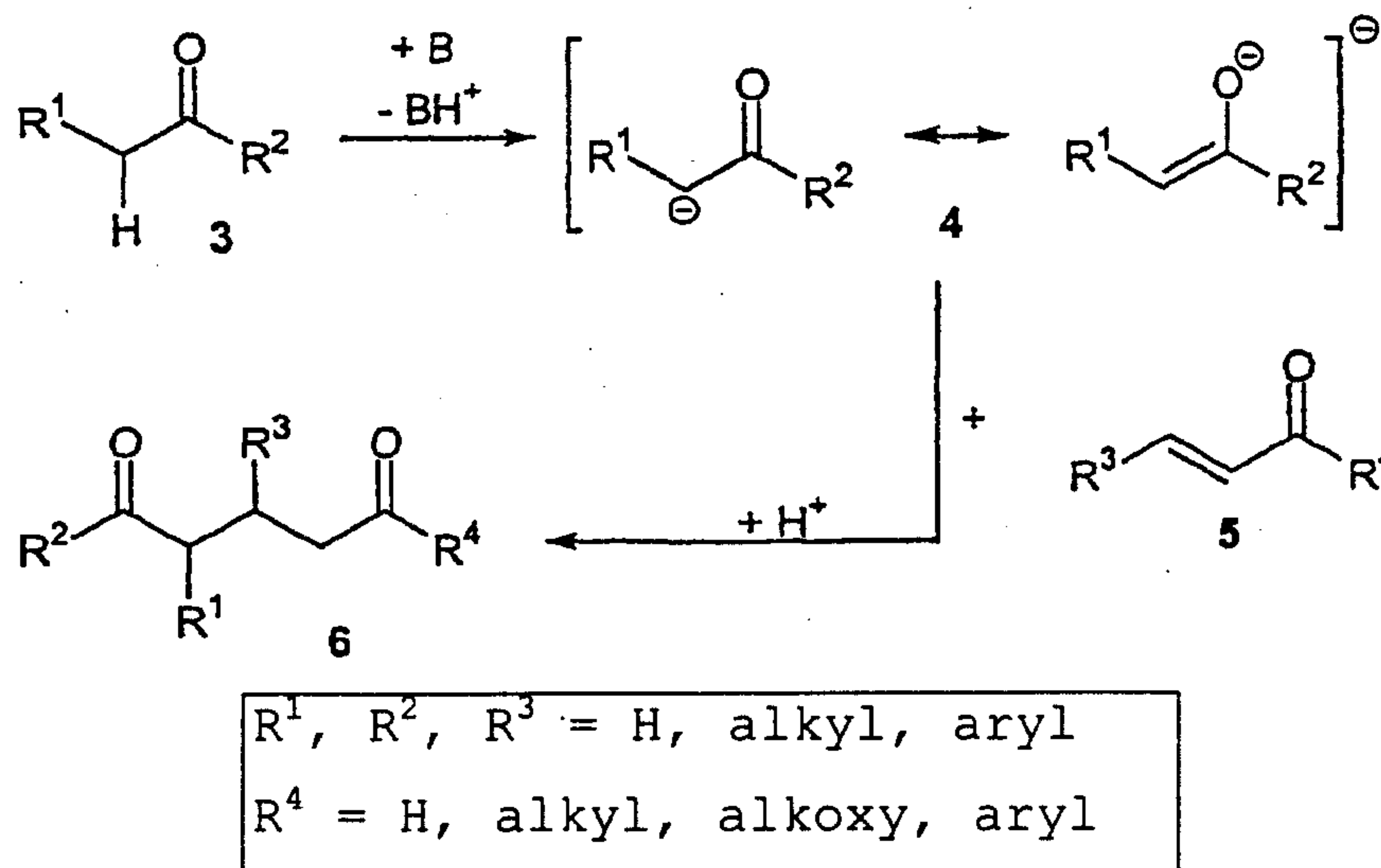
reactions. The reaction has enormous potential for synthesis.

Since there are many different kinds of *Michael* addition, some examples will be given in the following sections. Particular emphasis is placed here on *Michael* additions with thiols by asymmetric catalysis.

Conventional *Michael* addition

10

The conventional *Michael* reaction[6], as shown in Figure 4, is performed in protic solvents. In this reaction, a carbonyl compound 3 is deprotonated in α position with a base to form the enolate 4.



15

Figure 4: Conventional *Michael* addition.

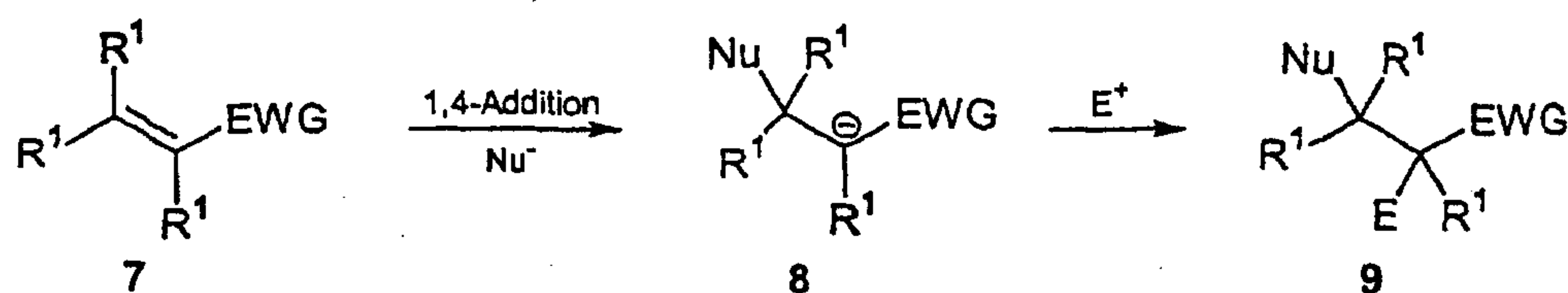
This enolate anion 4 (*Michael* donor) attacks in the form of a 1,4-addition onto an α,β -unsaturated carbonyl compound 5 (*Michael* acceptor). After reprotonation, the *Michael* adduct 6, a 1,5-diketone, is obtained.

The most important secondary reaction which may occur here is the aldol reaction [5]. The enolate anion formed then attacks, not in the β position, but instead directly on the

carbonyl oxygen of the *Michael* acceptor in the form of a 1,2-addition. The aldol reaction is here the kinetically favoured process, but this 1,2-addition is reversible. Since the *Michael* addition is irreversible, the more thermodynamically stable 1,4-adduct is obtained at elevated temperatures.

General *Michael* addition

There are now many related 1,4-additions in which the *Michael* acceptor and/or donor differ(s) from those used in the conventional *Michael* addition. They are frequently known as "*Michael* type" reactions or included in the superordinate term "*Michael* addition". Today, all 1,4-additions of a nucleophile (*Michael* donor) onto a C-C multiple bond (*Michael* acceptor) activated by electron-attracting groups are known as general *Michael* addition. In this reaction, the nucleophile is 1,4-added onto the activated C-C multiple bond 7 to form the adduct 8 (see Figure 5) [7].



EWG = electron withdrawing group Nu ⁻ = carbanion, S-, Se-, Si-, Sn-, O- or N-nucleophile E ⁺ = H, alkyl etc.
--

Figure 5: General *Michael* reactions.

25

When working in aprotic solvents, the intermediate carbanion 8 may be reacted with electrophiles to form 9

(E=H). If the electrophile is a proton, the reaction is known as a "normal" *Michael* addition. If, on the other hand, it is a carbon electrophile, it is known as a "Michael tandem reaction" as the 1,4-addition is followed
5 by the second step of the addition of the electrophile [8].

In addition to the α,β -unsaturated carbonyl compounds, it is also possible to use vinylogous sulfones [9], sulfoxides [10], phosphonates [11] and nitroolefins [12] as a *Michael*
10 acceptor. Nucleophiles which may be used are not only enolates, but also other carbanions together with other heteronucleophiles such as nitrogen [13], oxygen [14], silicon [15], tin [16], selenium [17] and sulfur [18].

15 Intramolecular control of *Michael* additions

Intramolecular control is one possible way of introducing asymmetric induction into the *Michael* addition of thiols on *Michael* acceptors. In this case, either the *Michael*
20 acceptor or the thiol already contains a stereogenic centre before reaction, the centre controlling the stereochemistry of the *Michael* reaction.

As can be seen in Figure 6, K. Tomioka et al. [19] have, in
25 a similar manner to Evans with oxazolidinones, used enantiopure N-acrylic acid pyrrolidinones to perform an induced *Michael* addition with thiols onto 2-alkyl acrylic acids:

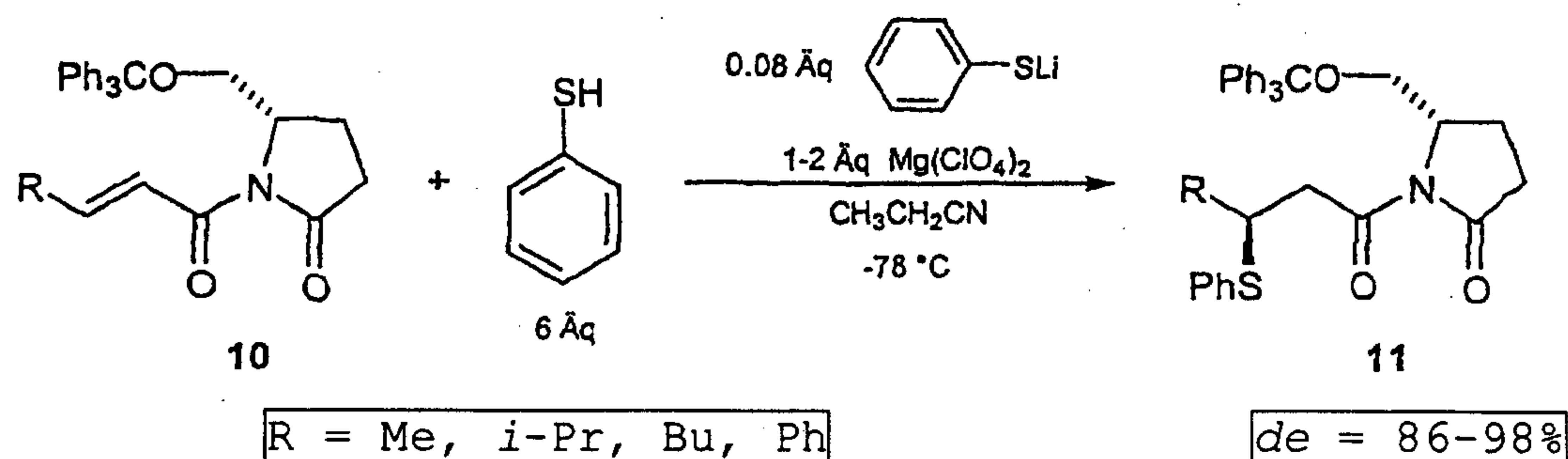


Figure 6: Asymmetric addition of thiophenol onto N-acrylic acid pyrrolidinone 10.

Key: Åq = eq.

The reaction was predetermined by the (*E/Z*) geometry of the acrylic pyrrolidinones. Asymmetric induction proceeds by the (*R*)-triphenylmethoxymethyl group in position 5 of the pyrrolidinone. This bulky "handle" covers the *Re* side of the double bond during the reaction, so that only the opposite *Si* side can be attacked. With individual addition of 0.08 equivalents of thiolate or $\text{Mg}(\text{ClO}_4)_2$, a *de* value of up to 70% could be achieved. With combined addition, the *de* value could even be raised to 98%. The *de* value is here taken to mean the proportion of pure enantiomer in the product, with the remainder to make up to 100% being the racemic mixture. The *ee* value has the same definition.

There are many further examples for synthesising a new stereogenic centre, but *Michael* additions of thiolates with intramolecular control in which two stereogenic centres are formed in a single step are rare.

T. Naito et al. [20] used the oxazolidinones from Evans [21] to introduce the chirality information into the *Michael* acceptor in a *Michael* addition in which two new centres were formed (Figure 7):

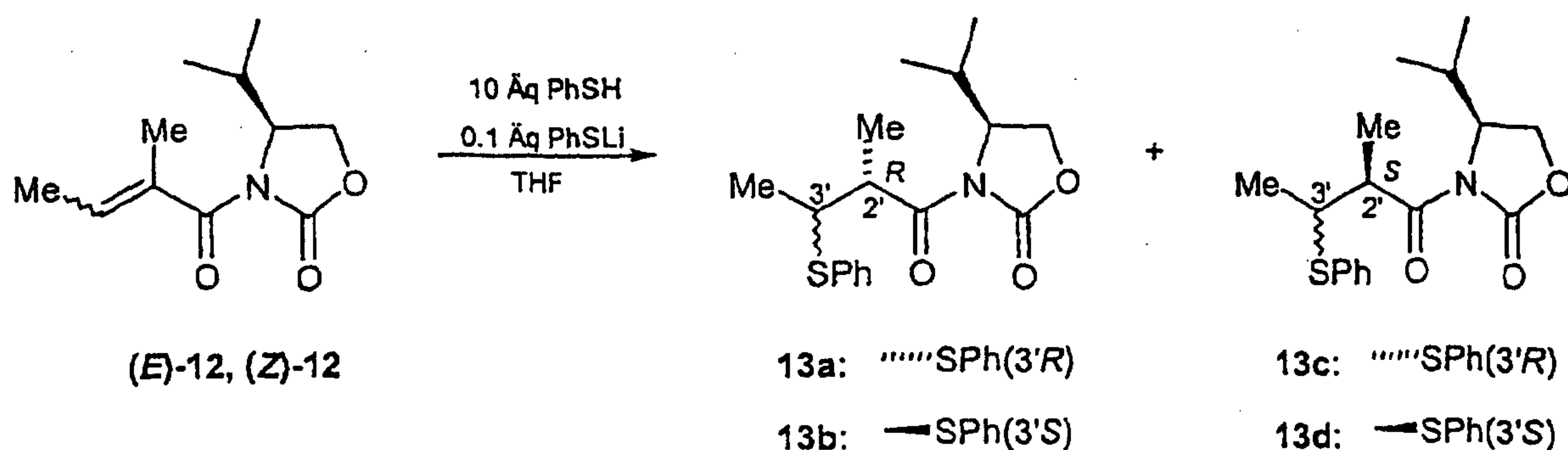


Figure 7: Michael addition with the formation of two stereogenic centres.

Key: Åq = eq.

5

Table 1: Test conditions and ratio of the two newly formed centres.

Educt	Yield [%]	Temp. [°C]	dr [%]			
			13a	13b	13c	13d
(E) -12	84	RT	>55	<1	<1	>43
(E) -12	98	-50	>89	<1	4	6
(E) -12	96	-50	>87	<1	4	8
(Z) -12	95	-30 - -10	3	4	<1	>92

10 In order to achieve elevated diastereomeric (80-86%) and enantiomeric (98%) excesses, a solution of 10 equivalents of thiophenol and 0.1 equivalents of lithium thiophenolate in THF was added at low temperatures (-50 - -10°C) to 1 equivalent of the chiral imide **12**. Since the methyl group

15 of **12** in 3' position was exchanged for a phenyl group, diastereomeric excesses of >80% were still obtained in the same reaction. The enantiomeric excesses, however, were still only between 0 and 50%. The stereocentre in 2' position could be selectively controlled in this case too,

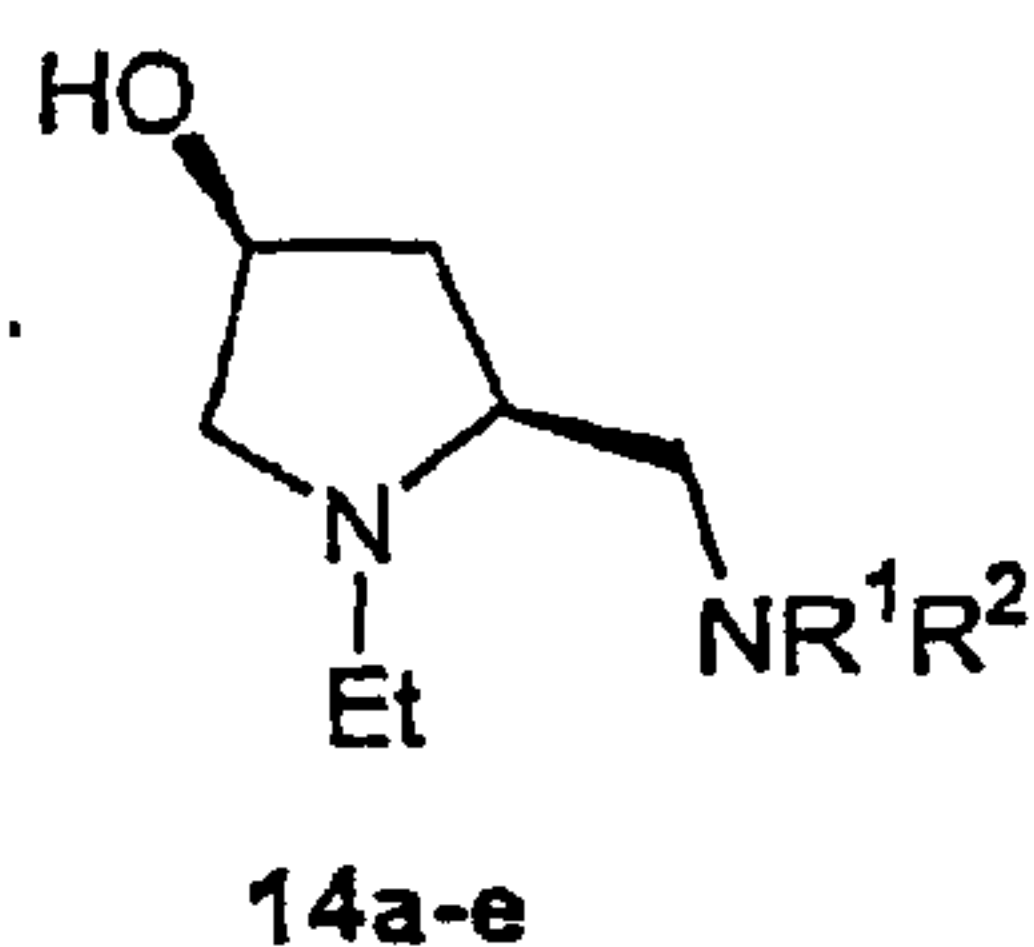
20 but only low levels of selectivity could be achieved on the centre in 3' position.

Michael addition catalysed by chiral bases

Michael addition of thiols onto α,β -unsaturated carbonyl compounds catalysed by bases such as triethylamine or piperidine has long been known [22]. When achiral educts are used, however, enantiopure bases are required in order to obtain optically active substances.

T. Mukaiyama et al. [23] investigated the use of hydroxyproline derivatives **14** as a chiral catalyst:

Table 2: Chiral hydroxyproline bases.



No.	R1	R2
14a	H	Phenyl
14b	H	Cyclohexyl
14c	H	1,5-Dimethylphenyl
14d	H	1-Naphthyl
14e	Me	Phenyl

The addition of thiophenol (0.8 equivalents) and cyclohexanone (1 equivalent) was investigated with the hydroxyproline derivatives **14a-e** (0.008 equivalents) in toluene. It was found that, when using **14d**, an ee value of 72% could be achieved.

PCT/EP01/10626

WO 02/22569

Many alkaloids were likewise tested for chiral base catalysis. Particularly frequent and extensive use was made of cinchona alkaloids [24],[25] and ephedrine alkaloids.

- 5 H. Wynberg [26] accordingly carried out very exhaustive testing of the *Michael* addition of thiophenol onto α,β -unsaturated cyclohexanones with cinchona and ephedrine alkaloids (see Figure 8) for catalysis and control:

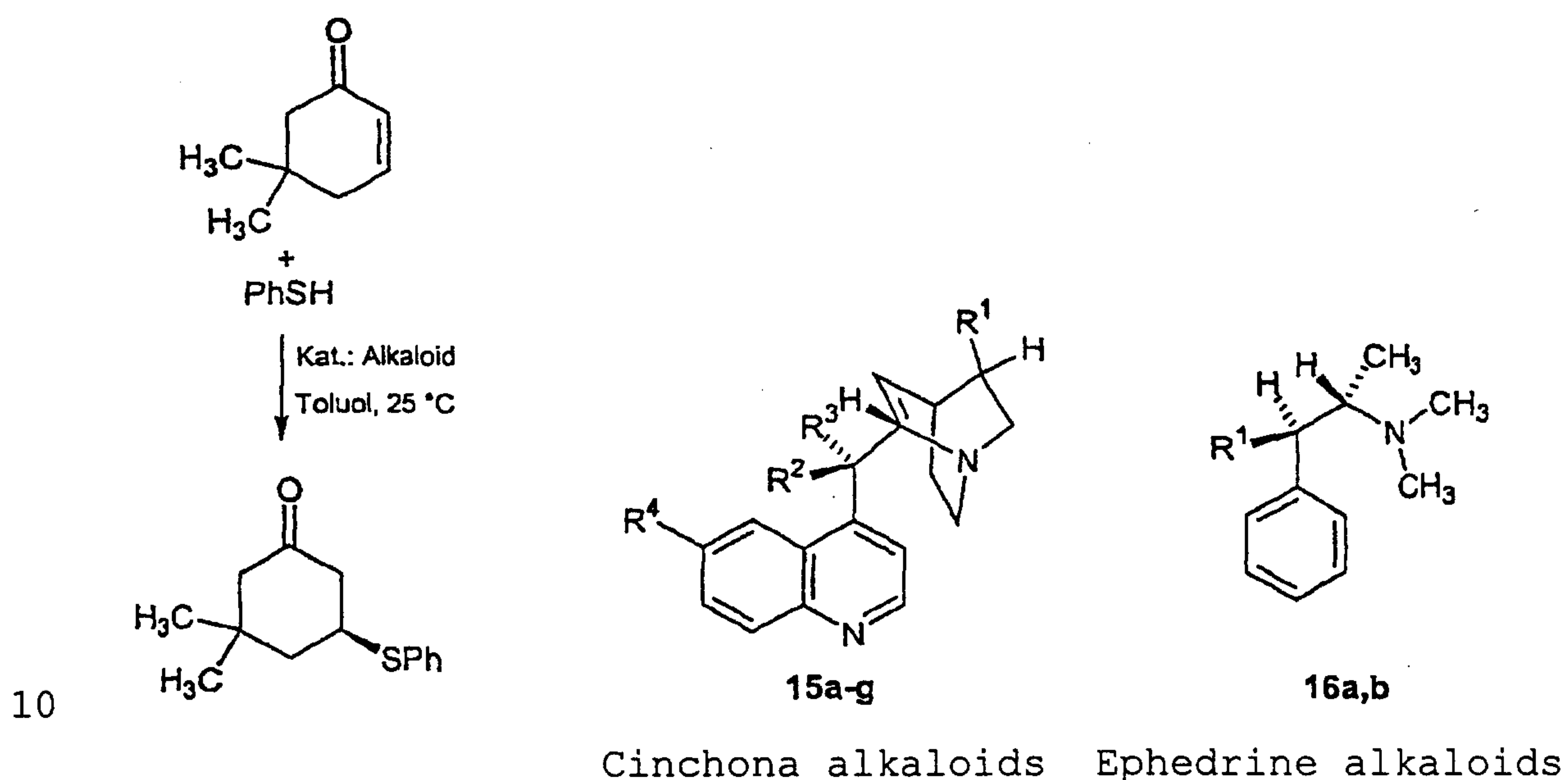


Figure 8: *Michael* reaction controlled by cinchona and ephedrine alkaloids.

- 15 Key: Kat. = cat; Alkaloid = alkaloid; Toluol = toluene.

Table 3: Enantiomeric excess when using various alkaloids in *Michael* addition.

No.	Name	R1	R2	R3	R4	ee [%]
<u>15a</u>	Quinine	C2H3	OH	H	OCH3	44
<u>15b</u>	Cinchonidine	C2H3	OH	H	H	62
<u>15c</u>	Dihydroquinine	C2H5	OH	H	OCH3	35
<u>15d</u>	Epiquinine	C2H3	H	OH	OCH3	18
<u>15e</u>	Acetylquinine	C2H3	OAc	H	OCH3	7
<u>15f</u>	Deoxycinchonidine	C2H3	H	H	H	4
<u>15g</u>	Epichlorocinchonidine	C2H3	H	Cl	H	3
<u>16a</u>	(-)-N-Methylephedrine	OH	-	-	-	29
<u>16b</u>	N,N-Dimethylamphetamine	H	-	-	-	0

5 As is clear from Table 3 even a slight change in the residues R1 - R4 in the alkaloid **15**, **16** brought about a distinct change in the enantiomeric excess. This means that the catalyst must be tailored to the educts. If, for example, p-methylthiophenol was used instead of thiophenol,
 10 a distinct worsening of the enantiomeric excess could be observed with the same catalyst.

Michael addition with chiral Lewis acid catalysis

15 Simple catalysis of the *Michael* addition of thiols onto *Michael* acceptors by simple Lewis acids, such as for example TiCl₄, sometimes with good yield, has long been known [27].

20 There are several examples of catalysis by chiral Lewis acids, in which, as also in the case of intramolecular control (section 1.2.3), N-acrylic acid oxazolidinones were used. However, this time, these do not contain a chiral

centre. The further carbonyl group of the introduced oxazolidinone ring is required to chelate the metal atom of the chiral Lewis acid $\rightarrow$ **17**. The Lewis acid **18** was used by D.A. Evans for the addition of silyl enol ethers onto the N-acrylic acid oxazolidinone **17** + Lewis acid complex **18** with diastereomeric excesses of 80-98% and enantiomeric excesses of 75-99% (see Figure 9) [28].

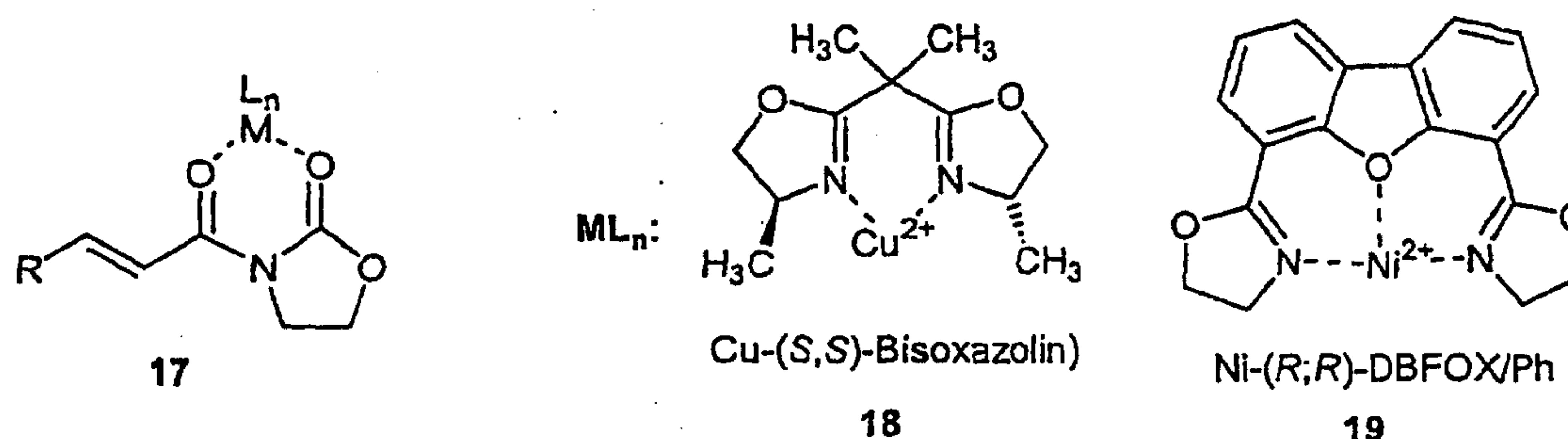


Figure 9: Chiral Lewis acids **18** + **19**, which bind to the N-acrylic acid oxazolidinone **17**.

Key: Cu-(S,S)-Bisoxazolin = Cu (S,S)-bisoxazoline

The Lewis acid Ni-(R,R)-DBFOX/Ph (DBFOX/Ph = 4,6-dibenzofurandiyl-2,2'-bis-(4-phenyloxazoline)) **19** was used by S. Kanemasa for the addition of thiols onto **17** [29]. He achieved enantiomeric excesses of up to 97% with good yields.

In many instances, 1,1-binaphthols (binol) were also bound to metal ions in order to form chiral Lewis acids (see Figure 10). B. L. Feringa [30] accordingly synthesised an LiAl binol complex **20**, which he used in a *Michael* addition of α -nitro esters onto α,β -unsaturated ketones. At -20°C in THF, when using 10 mol% of LiAl binol **20**, he obtained *Michael* adducts with an ee of up to 71%.

Shibasaki [31] uses the NaSm binol complex **21** in the *Michael* addition of thiols onto α,β -unsaturated acyclic

ketones. At -40°C , he obtained *Michael* adducts with enantiomeric excesses of 75-93%.

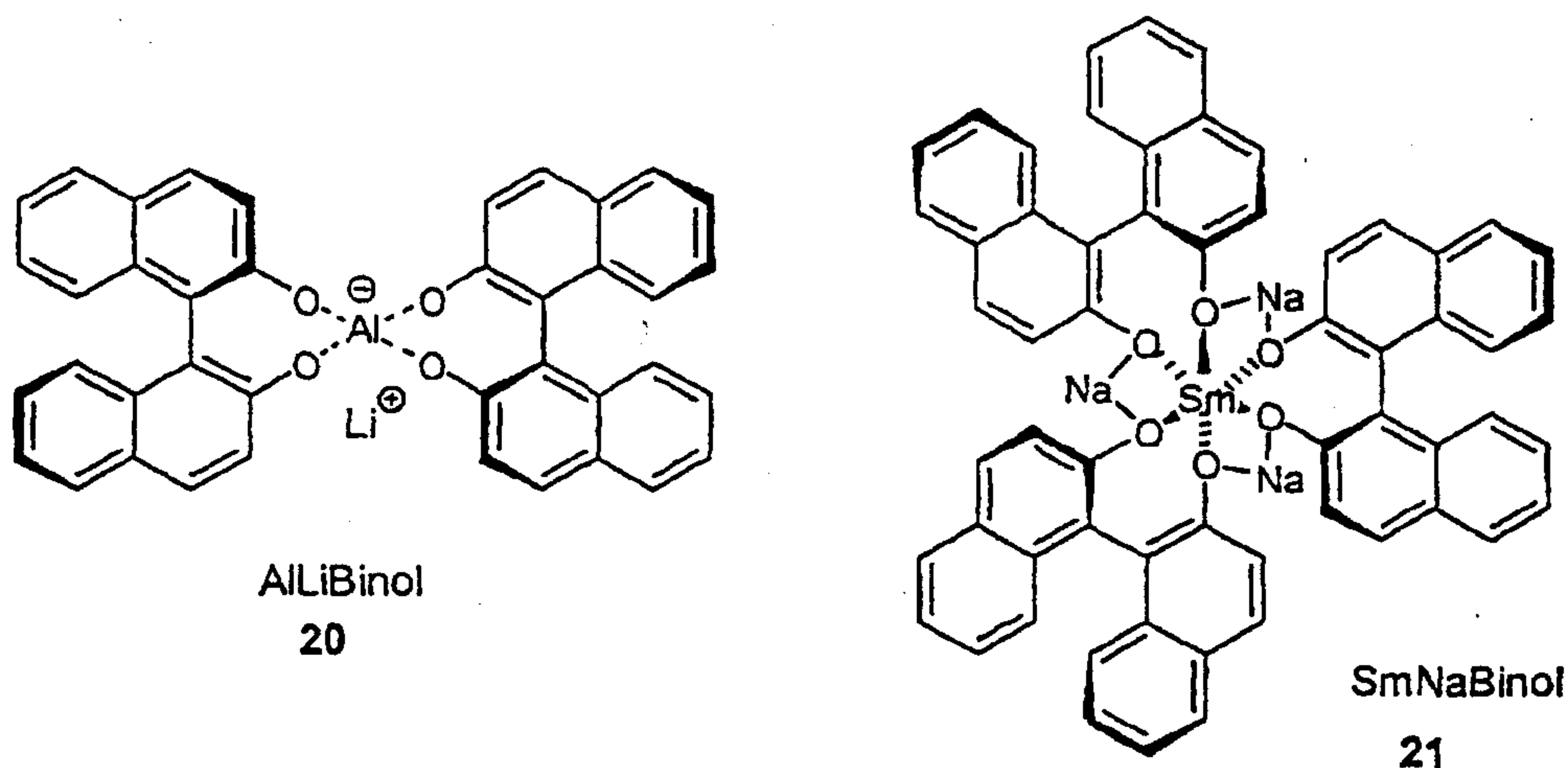


Figure 10: (R,R)-binaphthol complexes of aluminium and samarium.

On addition of the *Michael* donor and acceptor, these chiral Lewis acids form a diastereomorphous transition state, by means of which the reaction is then controlled.

Control of *Michael* addition by complexation of the lithiated nucleophile

Another way of controlling the attack of a nucleophile (*Michael* donor) in a reaction is to complex the lithiated nucleophile by an external chiral ligand.

Tomiooka et al.^[32] have tested many external chiral ligands for controlled attack of organometallic compounds in various reactions, such as for example, aldol additions, alkylations of enolates, *Michael* additions, etc.. Figure 11 shows several examples of enantiomerically pure compounds with which *Tomiooka* complexed organometallic compounds.

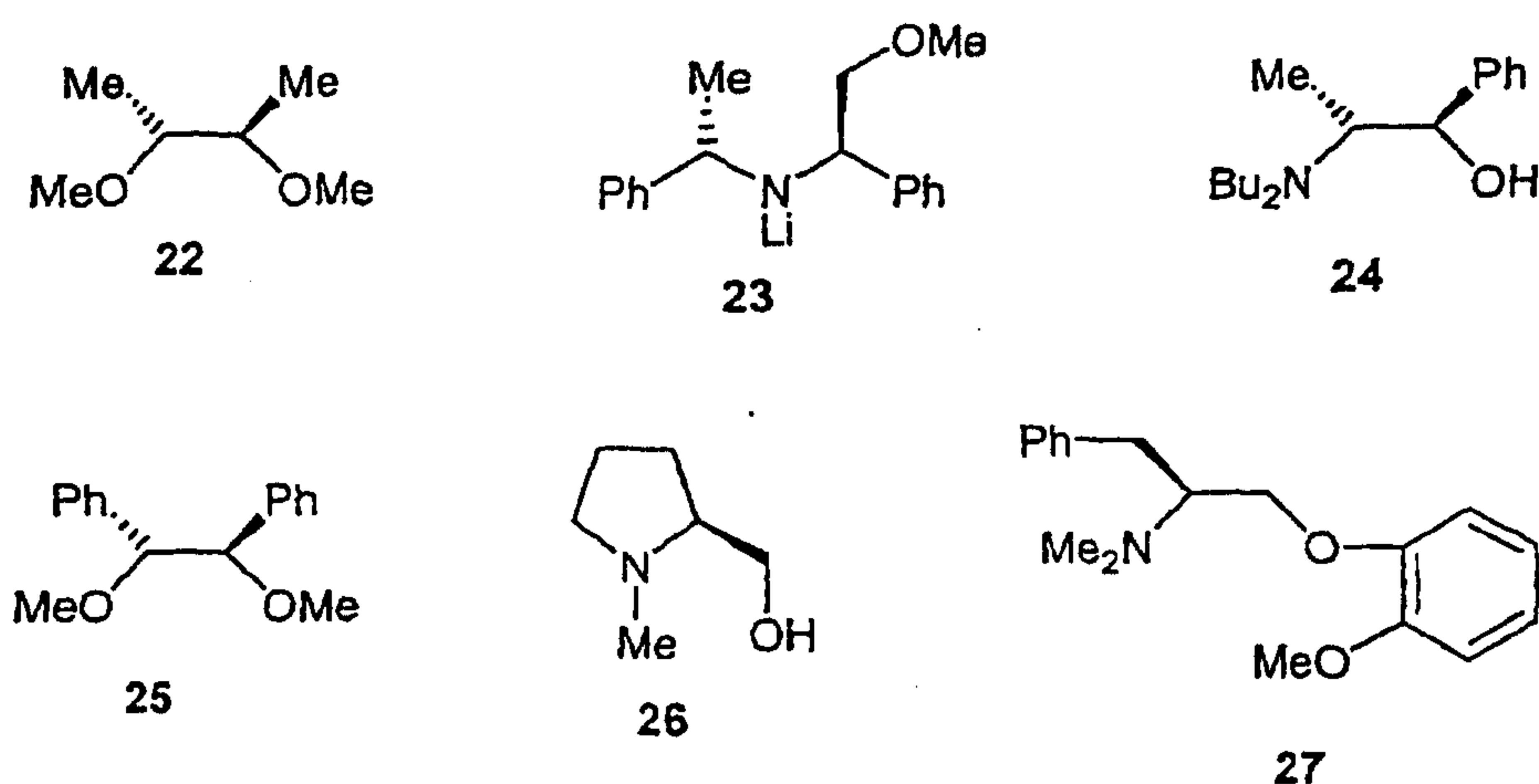


Figure 11: Examples of enantiopure ligands for controlling the attack of organolithium compounds.

5 For example, using dimethyl ether **22**, he controlled the aldol addition of dimethylmagnesium onto benzaldehyde and obtained an enantiomeric excess of 22%. In contrast, with lithium amide **23**, he achieved an enantiomeric excess of 90% in the addition of BuLi onto benzaldehyde. With **24**, he
 10 achieved enantiomeric excesses of 90% in the addition of diethylzinc onto benzaldehyde. Using the proline derivative **26**, he controlled the addition of organometallic compounds onto Michael systems with enantiomeric excesses of up to 90%. Using **27**, he was only able to achieve an ee of 50% in
 15 the alkylation of cyclic enamines.

Tomioka subsequently extended his synthesis, by using not only organolithium compounds, but also lithium thiolates^[33]. He used chiral dimethyl ethers such as for example **25**,
 20 sparteine or chiral diethers for this purpose. This latter is related to **27** and, thanks to a phenyl substituent in 2 position, has a further chiral centre. In a Michael addition of lithium thiolates onto methyl acrylates enantiomeric excesses of 90% could be achieved for these
 25 chiral diethers, but only of 6% for **25**.

If it is considered that in every case the chiral compounds are used in only catalytic quantities of 5-10 mol%, some of these enantiomeric excesses should be deemed very good.

5

Tomioka proposed the concept of the asymmetric oxygen atom for the dimethyl ethers 28 in nonpolar solvents ^[34]:

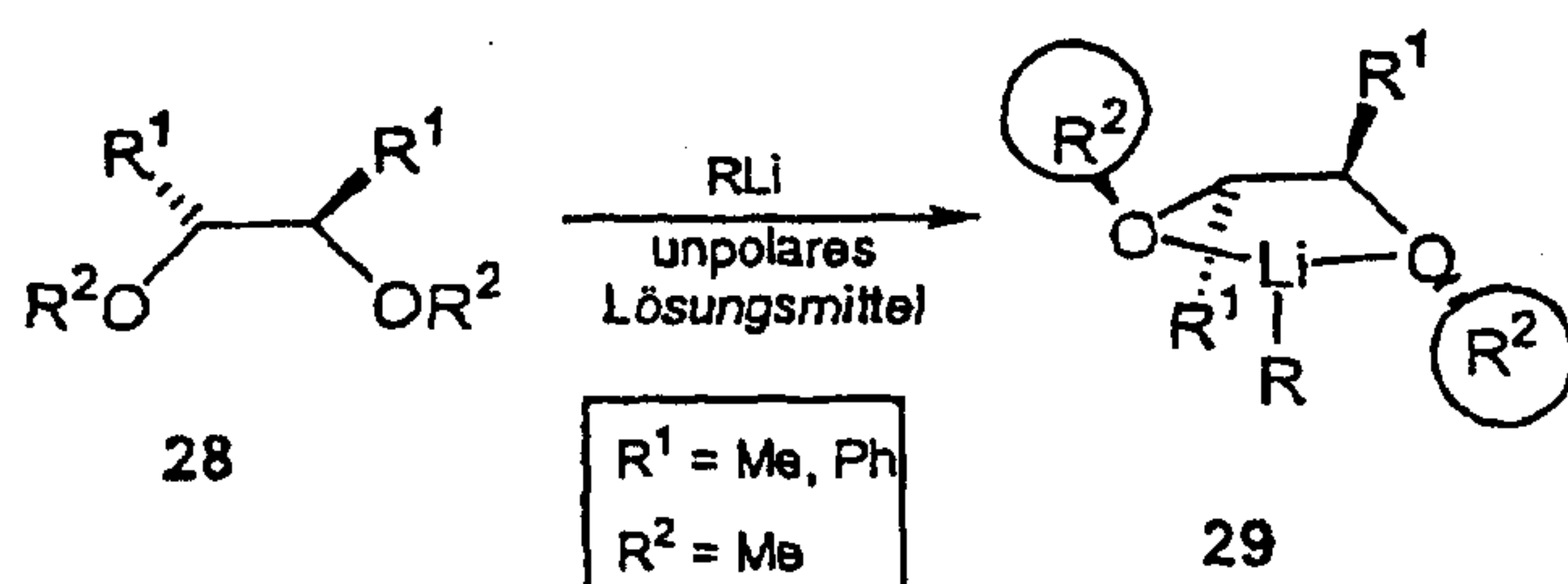


Figure 12: Model of a chiral chelate of organolithium compounds.

10

Key: unpolares Lösungsmittel = nonpolar solvent

As shown in Figure 12, due to steric effects, the residues of 28 in the complex 29 are in *all-trans* position. Thanks to the asymmetric carbon atoms in the ethylene bridge, the adjacent oxygen atoms become asymmetric centres. According to X-ray structural analysis, these oxygen atoms, which chelate the lithium, in 29 are tetrahedrally coordinated. The chirality information is thus provided directly adjacent to the chelating lithium atom by the bulky residue R2.

20

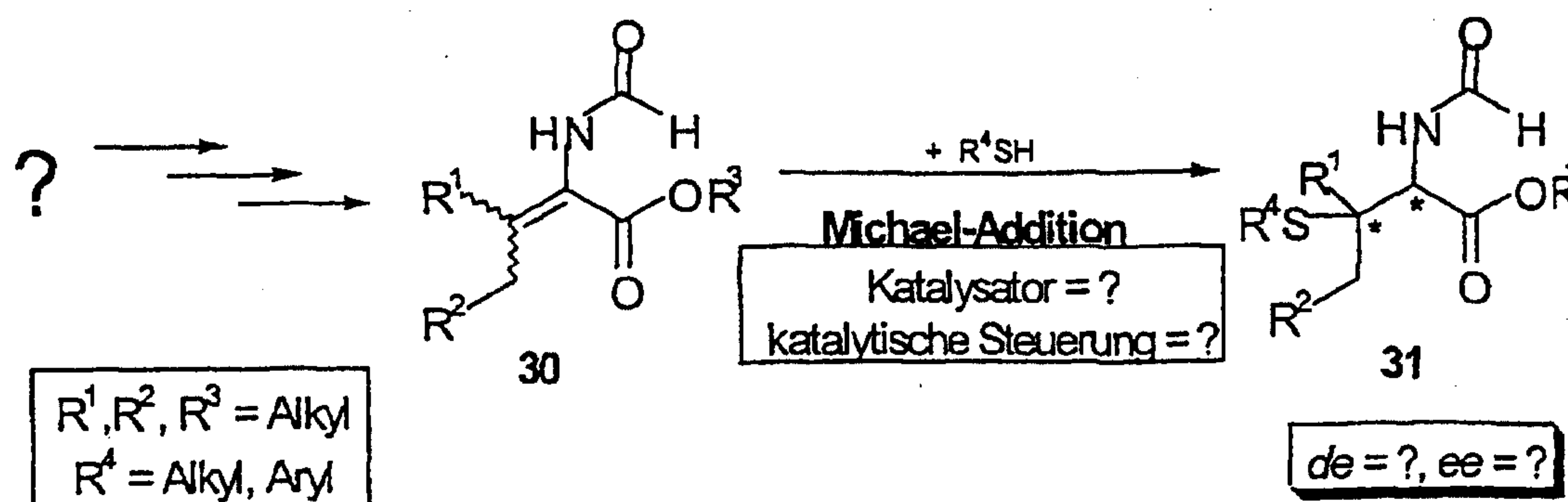
The object of the invention was in general to develop an asymmetric synthesis under Michael addition conditions, which synthesis avoids certain disadvantages of the prior art and provides good yields.

25

Specifically, the object was to provide a simple synthetic pathway for producing 2-formylamino-3-dialkyl acrylic acid esters 30 and for separating from one another the (*E,Z*)

30

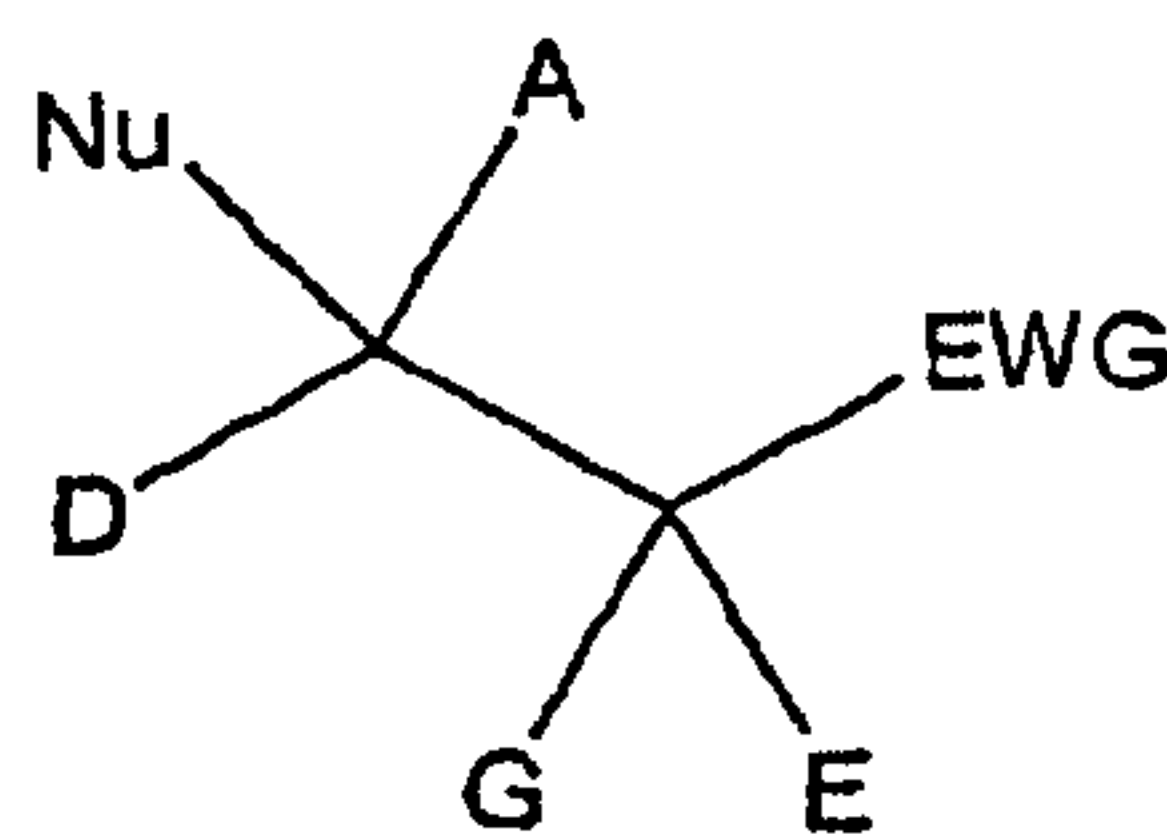
mixtures of the acrylic acid esters **30** which are formed. A further object was, on the basis of the synthesised *Michael* acceptor **30**, to find a pathway for *Michael* addition with thiols. It would first be necessary to find a Lewis acid catalyst for this addition, which catalyst can subsequently be provided with chiral ligands for control (see Figure 13), so directly determining the diastereomeric and enantiomeric excesses of the *Michael* adducts **31**.



10 **Figure 13: Object**

Key: Katalysator = catalyst; katalytische Steuerung = catalytic control

The invention accordingly generally provides a process for the production of a compound of the general formula **9**

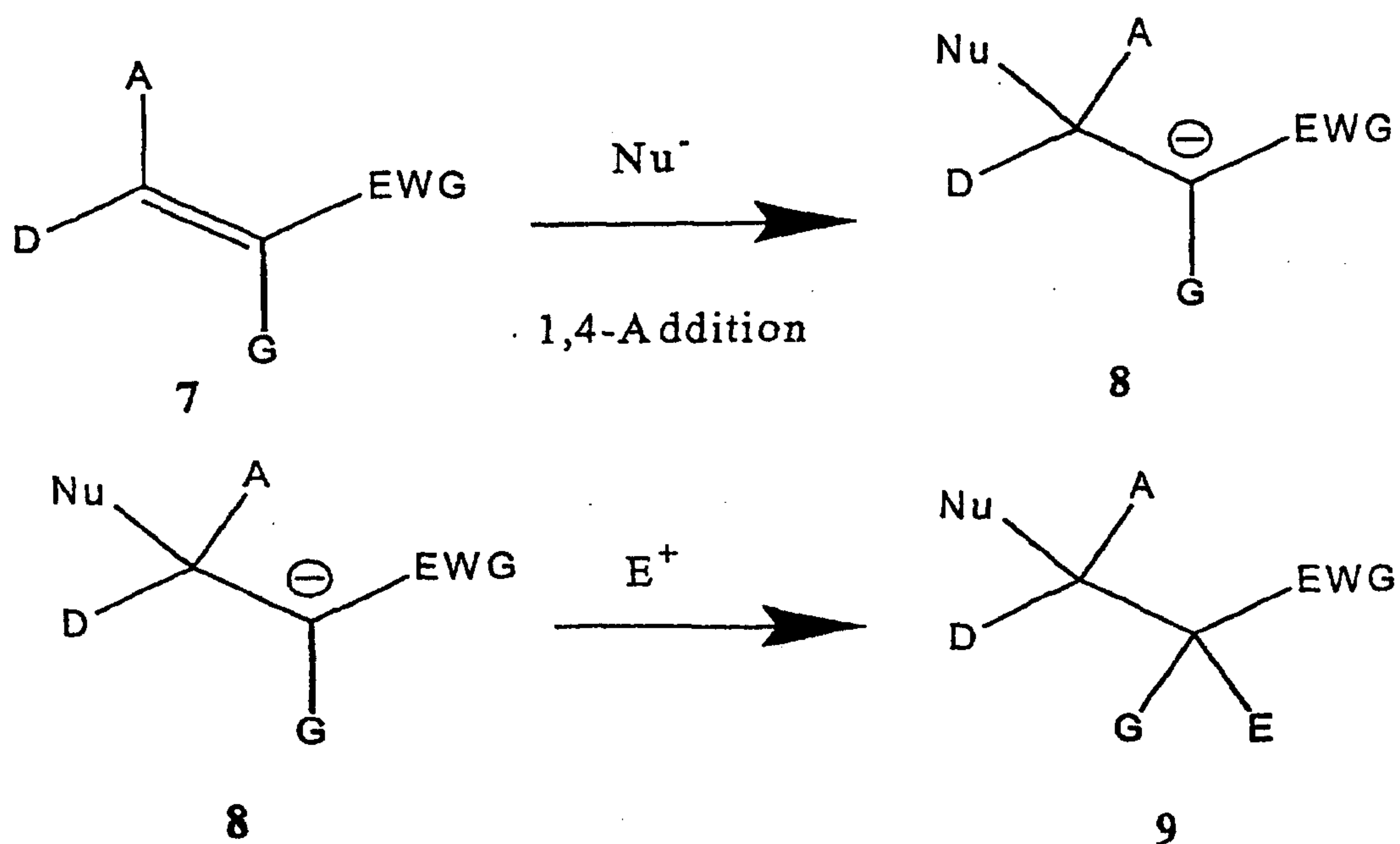


15

wherein a compound of the general formula **7** is reacted under suitable 1,4-*Michael* addition conditions with a nucleophile Nu^- according to the following reaction scheme

PCT/EP01/10626

WO 02/22569



in which the residues

A, D and G are mutually independently identical or different and represent any desired substituents,

5 E is selected from among H or alkyl,

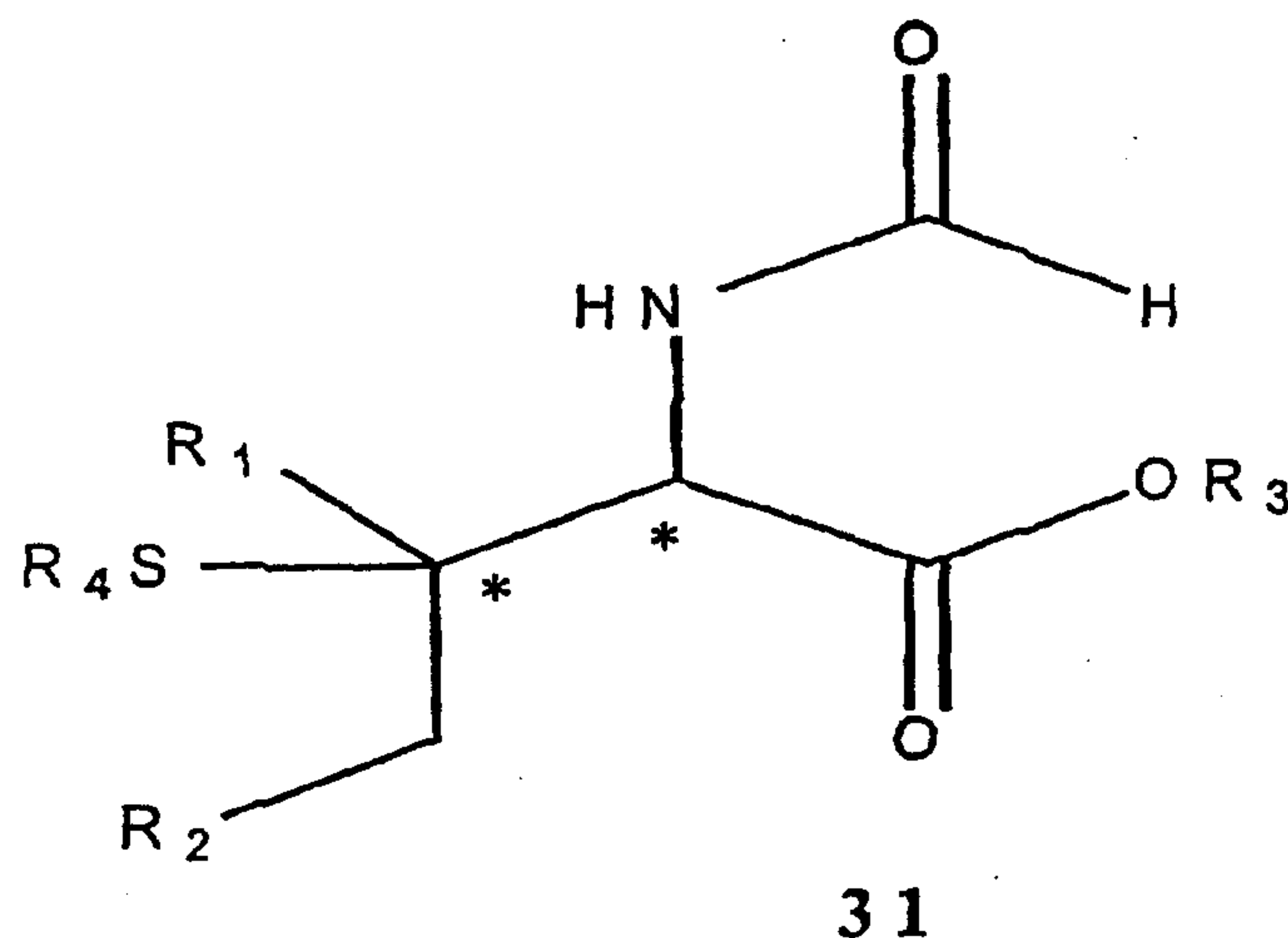
Nu is selected from among a C-, S-, Se-, Si-, Si-, O- or N-nucleophile,

and EWG denotes an electron-attracting group,

10 characterised in that the conditions are selected such that the stereoisomeric, in particular enantiomeric and/or diastereomeric, products are obtained in unequal quantities. It is particularly preferred if the nucleophile Nu^- is an S-nucleophile.

15

The invention specifically also provides a process for the production of a compound of the general formula 31



in which

R1, R2 and R3 are mutually independently selected from
among

C₁₋₁₀ alkyl, saturated or unsaturated, branched or
unbranched, mono- or polysubstituted or unsubstituted;
and

* indicates a stereoselective centre

R4 is selected from among:

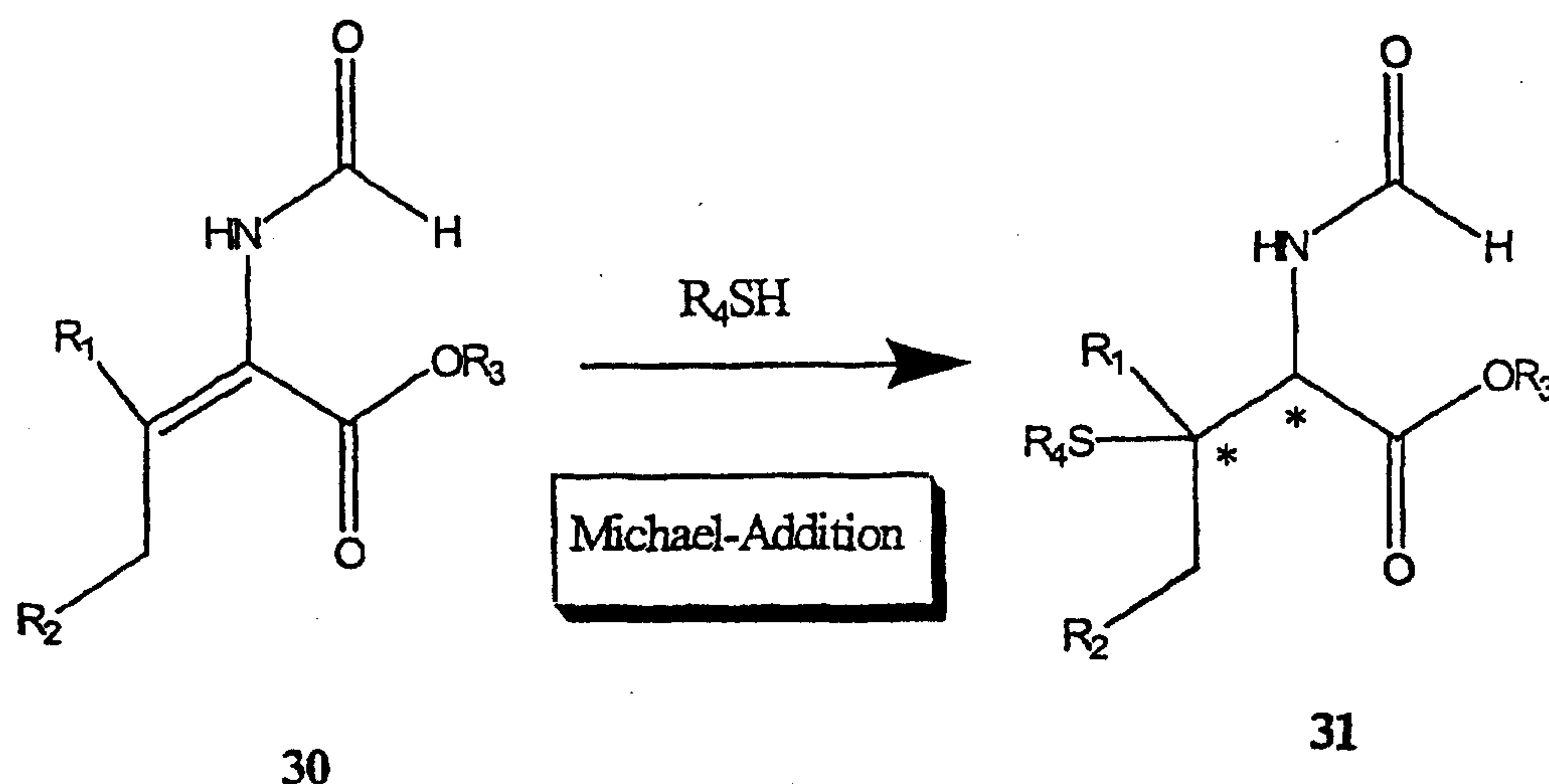
C₁₋₁₀ alkyl, saturated or unsaturated, branched or
unbranched, mono- or polysubstituted or unsubstituted;
C₃₋₈ cycloalkyl, saturated or unsaturated,
unsubstituted or mono- or polysubstituted; aryl or
heteroaryl, in each case unsubstituted or mono- or
polysubstituted; or aryl, C₃₋₈ cycloalkyl or
heteroaryl, in each case unsubstituted or mono- or
polysubstituted, attached via saturated or unsaturated
C₁₋₃ alkyl;

in which a compound of the general formula 30, is reacted
under Michael addition conditions with a compound of

PCT/EP01/10626

WO 02/22569

the general formula R_4SH , in accordance with reaction I below:



Reaction I

5 wherein the compounds of the formula R_4SH are used as lithium thiolates or are converted into lithium thiolates during or before reaction I and/or chiral catalysts, selected from among: chiral auxiliary reagents, in particular the diether (S,S)-1,2-

10 dimethoxy-1,2-diphenylethane; Lewis acids and/or Brønsted bases or combinations thereof are used, and are optionally then hydrolysed with bases, in particular NaOH, and optionally purified, preferably by column chromatography.

15

For the purposes of the present invention alkyl or cycloalkyl residues are taken to mean saturated and unsaturated (but not aromatic), branched, unbranched and cyclic hydrocarbons, which may be unsubstituted or mono- or

20 polysubstituted. C_{1-2} alkyl here denotes C1 or C2 alkyl, C_{1-3} alkyl denotes C1, C2 or C3 alkyl, C_{1-4} alkyl denotes C1, C2, C3 or C4 alkyl, C_{1-5} alkyl denotes C1, C2, C3, C4 or C5 alkyl, C_{1-6} alkyl denotes C1, C2, C3, C4, C5 or C6 alkyl, C_{1-7} alkyl denotes C1, C2, C3, C4, C5, C6 or C7 alkyl, C_{1-8}

25 alkyl denotes C1, C2, C3, C4, C5, C6, C7 or C8 alkyl, C_{1-10}

PCT/EP01/10626

WO 02/22569

alkyl denotes C1, C2, C3, C4, C5, C6, C7, C8, C9 or C10
alkyl and C₁₋₁₈ alkyl denotes C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, C15, C16, C17 or C18 alkyl.
C₃₋₄ cycloalkyl furthermore denotes C3 or C4 cycloalkyl, C₃₋₅
5 cycloalkyl denotes C3, C4 or C5 cycloalkyl, C₃₋₆ cycloalkyl denotes C3, C4, C5 or C6 cycloalkyl, C₃₋₇ cycloalkyl denotes C3, C4, C5, C6 or C7 cycloalkyl, C₃₋₈ cycloalkyl denotes C3, C4, C5, C6, C7 or C8 cycloalkyl, C₄₋₅ cycloalkyl denotes C4 or C5 cycloalkyl, C₄₋₆ cycloalkyl denotes C4, C5 or C6
10 cycloalkyl, C₄₋₇ cycloalkyl denotes C4, C5, C6 or C7 cycloalkyl, C₅₋₆ cycloalkyl denotes C5 or C6 cycloalkyl and C₅₋₇ cycloalkyl denotes C5, C6 or C7 cycloalkyl. With regard to cycloalkyl, the term also includes saturated cycloalkyls in which one or 2 carbon atoms are replaced by a heteroatom
15 S, N or O. The term cycloalkyl in particular, however, also includes mono- or polyunsaturated, preferably monounsaturated, cycloalkyls without a heteroatom in the ring, provided that the cycloalkyl does not constitute an aromatic system. The alkyl or cycloalkyl residues are
20 preferably methyl, ethyl, vinyl (ethenyl), propyl, allyl (2-propenyl), 1-propynyl, methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, hexyl, 1-methylpentyl, cyclopropyl, 2-methylcyclopropyl,
25 cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cycloheptyl, cyclooctyl, as well as adamantyl, CHF₂, CF₃ or CH₂OH and pyrazolinone, oxopyrazolinone, [1,4]-dioxane or dioxolane.

30 In relation to alkyl and cycloalkyl, it is here understood that, unless explicitly stated otherwise, for the purposes of the present invention, substituted means the substitution at least one hydrogen residue by F, Cl, Br, I, NH₂, SH or OH, wherein "polysubstituted" residues should be

PCT/EP01/10626

WO 02/22569

taken to mean that substitution is performed repeatedly both on different and the same C atoms with identical or different substituents, for example three times on the same C atom as in case of CF_3 or on different sites as in the case of $-\text{CH}(\text{OH})-\text{CH}=\text{CH}-\text{CHCl}_2$. Particularly preferred substituents are here F, Cl and OH. With regard to cycloalkyl, the hydrogen residue may also be replaced by OC_{1-3} alkyl or C_{1-3} alkyl (in each case mono- or polysubstituted or unsubstituted), in particular methyl, ethyl, n-propyl, i-propyl, CF_3 , methoxy or ethoxy.

The term $(\text{CH}_2)_{3-6}$ should be taken to mean $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ and $\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, while $(\text{CH}_2)_{1-4}$ should be taken to mean $-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ and $(\text{CH}_2)_{4-5}$ should be taken to mean $\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, etc..

An aryl residue is taken to mean ring systems comprising at least one aromatic ring, but without a heteroatom in even one of the rings. Examples are phenyl, naphthyl, fluoranthenyl, fluorenyl, tetralinyl or indanyl, in particular 9H fluorenyl or anthacenyl residues, which may be unsubstituted or mono- or polysubstituted.

25

A heteroaryl residue is taken to mean heterocyclic ring systems comprising at least one unsaturated ring, which contain one or more heteroatoms from the group comprising nitrogen, oxygen and/or sulfur and may also be mono- or polysubstituted. Examples from the group of heteroaryls which may be mentioned are furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, pyrimidine, pyrazine, quinoline, isoquinoline, phthalazine, benzo-1,2,5-thiadiazole, benzothiazole, indole, benzotriazole,

PCT/EP01/10626

WO 02/22569

benzodioxolane, benzodioxane, carbazole, indole and quinazoline.

In relation to aryl and heteroaryl, substituted is taken to mean the substitution of the aryl or heteroaryl with R^{23} , OR^{23} , a halogen, preferably F and/or Cl, a CF_3 , a CN, an NO_2 , an $NR^{24}R^{25}$, a C_{1-6} alkyl (saturated), a C_{1-6} alkoxy, a C_{3-8} cycloalkoxy, a C_{3-8} cycloalkyl or a C_{2-6} alkylene.

10 The residue R^{23} here denotes H, a C_{1-10} alkyl, preferably a C_{1-6} alkyl, an aryl or heteroaryl or an aryl or heteroaryl residue attached via a C_{1-3} alkylene group, wherein these aryl or heteroaryl residues may not themselves be substituted with aryl or heteroaryl residues,

15 the residues R^{24} and R^{25} , identical or different, denote H, a C_{1-10} alkyl, preferably a C_{1-6} alkyl, an aryl, a heteroaryl or an aryl or heteroaryl attached via a C_{1-3} alkylene group, wherein these aryl and heteroaryl residues may not themselves be substituted with aryl or heteroaryl residues,

or the residues R^{24} and R^{25} together mean $CH_2CH_2OCH_2CH_2$, $CH_2CH_2NR^{26}CH_2CH_2$ or $(CH_2)_{3-6}$, and

25 the residue R^{26} denotes H, a C_{1-10} alkyl, preferably a C_{1-6} alkyl, an aryl or heteroaryl residue or denotes an aryl or heteroaryl residue attached via a C_{1-3} alkylene group, wherein these aryl or heteroaryl residues may not themselves be substituted with aryl or heteroaryl residues.

30

In a preferred embodiment of the process according to the invention, the compounds of the formula R_4SH are used as lithium thiolates or are converted into lithium thiolates during or before reaction I.

In a preferred embodiment of the process according to the invention, butyllithium (BuLi) is used before reaction I to convert the compounds of the formula R_4SH into lithium
5 thiolates, preferably in an equivalent ratio of BuLi: R_4SH of between 1:5 and 1:20, in particular 1:10, and is reacted with R_4SH and/or the reaction proceeds at temperatures of $\leq 0^\circ C$ and/or in an organic solvent, in particular toluene, ether, THF or DCM, especially THF.

10

In a preferred embodiment of the process according to the invention, at the beginning of reaction I, the reaction temperature is at temperatures of $\leq 0^\circ C$, preferably at between -70 and $-80^\circ C$, in particular $-78^\circ C$, and, over the
15 course of reaction I, the temperature is adjusted to room temperature or the reaction temperature at the beginning of reaction I is at temperatures of $\leq 0^\circ C$, preferably at between -30 and $-20^\circ C$, in particular $-25^\circ C$, and, over the course of reaction I, the temperature is adjusted to
20 between $-20^\circ C$ and $-10^\circ C$, in particular $-15^\circ C$.

In a preferred embodiment of the process according to the invention, reaction I proceeds in an organic solvent, preferably toluene, ether, THF or DCM, in particular in
25 THF, or a nonpolar solvent, in particular in DCM or toluene.

In a preferred embodiment of the process according to the invention, the diastereomers are separated after reaction
30 I, preferably by preparative HPLC or crystallisation, in particular using the solvent pentane/ethanol (10:1) and cooling.

PCT/EP01/10626

WO 02/22569

In a preferred embodiment of the process according to the invention, separation of the enantiomers proceeds before separation of the diastereomers.

5 In a preferred embodiment of the process according to the invention, R^1 means C_{1-6} alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted, and R^2 means C_{2-9} alkyl, saturated or unsaturated, branched or unbranched, mono- or
10 polysubstituted or unsubstituted;

preferably

R^1 means C_{1-2} alkyl, mono- or polysubstituted or
15 unsubstituted,

in particular methyl or ethyl, and R^2 means C_{2-9} alkyl, preferably C_{2-7} alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or
20 unsubstituted, in particular ethyl, propyl, n-propyl, i-propyl, butyl, n-butyl, i-butyl, tert.-butyl, pentyl, hexyl or heptyl;

in particular

25 residue R^1 means methyl and R^2 means n-butyl.

In a preferred embodiment of the process according to the invention, R^3 is selected from among C_{1-3} alkyl, saturated or
30 unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted, preferably methyl or ethyl.

PCT/EP01/10626

WO 02/22569

In a preferred embodiment of the process according to the invention, R^4 is selected from among C_{1-6} alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; phenyl or thiophenyl, unsubstituted or monosubstituted (preferably with OCH_3 , CH_3 , OH , SH , CF_3 , F , Cl , Br or I); or phenyl attached via saturated CH_3 , unsubstituted or monosubstituted (preferably with OCH_3 , CH_3 , OH , SH , CF_3 , F , Cl , Br or I);

10 R^4 is preferably selected from among C_{1-6} alkyl, saturated, unbranched and unsubstituted, in particular methyl, ethyl, propyl, n-propyl, i-propyl, butyl, n-butyl, i-butyl, tert.-butyl, pentyl or hexyl; phenyl or thiophenyl, unsubstituted or monosubstituted
15 (preferably with OCH_3 , CH_3 , OH , SH , CF_3 , F , Cl , Br or I); or phenyl attached via saturated CH_3 , unsubstituted or monosubstituted (preferably with OCH_3 , CH_3 , OH , SH , CF_3 , F , Cl , Br or I),
20 in particular R^4 is selected from among methyl, ethyl or benzyl, unsubstituted or monosubstituted (preferably with OCH_3 , CH_3 , OH , SH , CF_3 , F , Cl , Br or I).

25 In a preferred embodiment of the process according to the invention, the thiolate is used stoichiometrically, $TMSCl$ is used and/or a chiral proton donor R^*-H is then used,

or

30

compound **30** is modified before reaction I with a sterically demanding (large) group, preferably TBDMS.

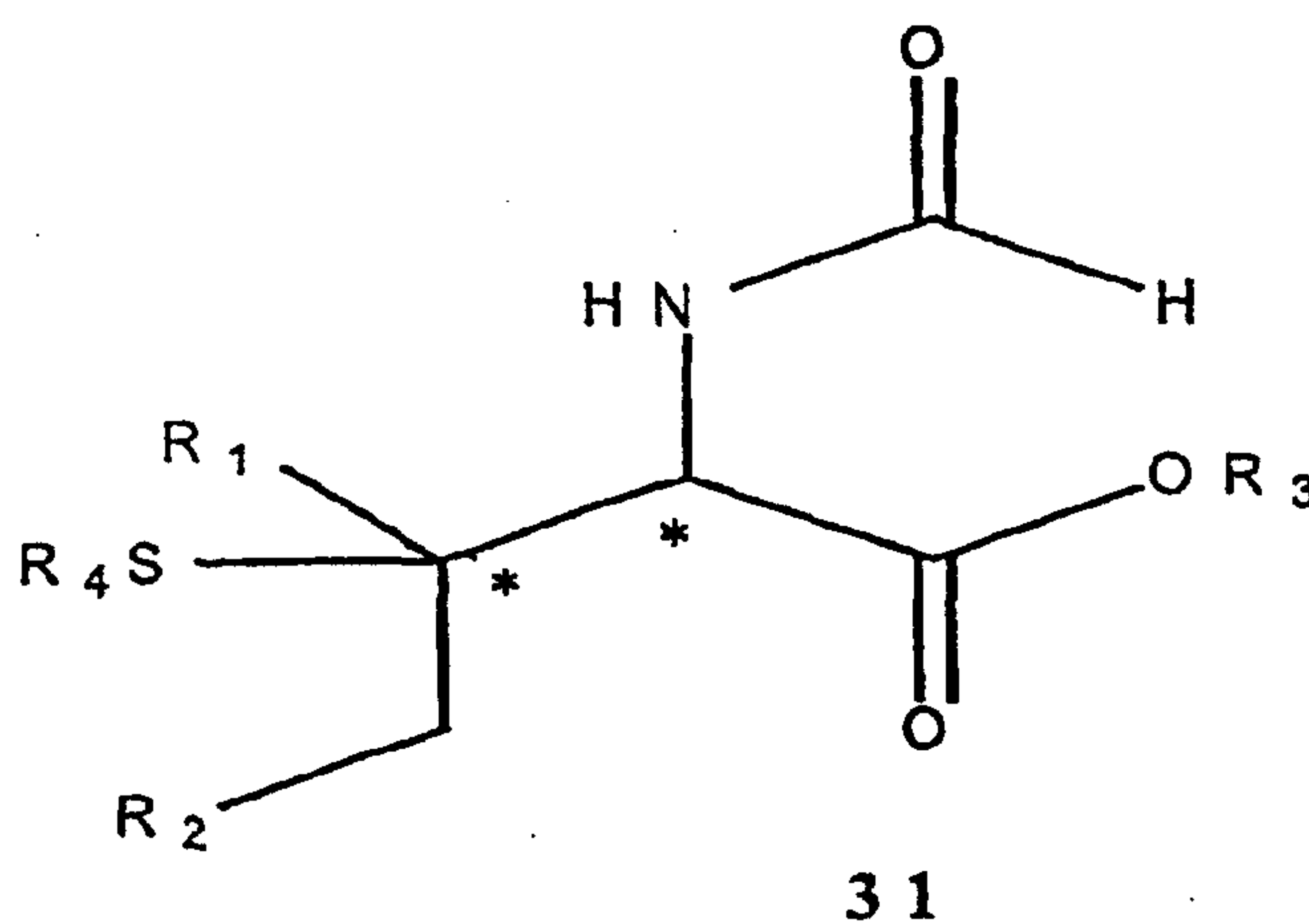
PCT/EP01/10626

WO 02/22569

In a preferred embodiment of the process according to the invention, the compound of the general formula 31 is 3-ethylsulfanyl-2-formylamino-3-methyloctanoic acid ethyl ester or 3-benzylsulfanyl-2-formylamino-3-methyloctanoic acid ethyl ester, the compound of the general formula 30 is 2-formylamino-3-methyl-2-octenoic acid ethyl ester and R₄SH is ethyl mercaptan or benzyl mercaptan.

The other conditions and embodiments of *Michael* addition, as explained below, are furthermore also preferred embodiments of the process according to the invention.

The invention also provides a compound of the general formula 31



in which

R₁, R₂ and R₃ are mutually independently selected from among C₁₋₁₀ alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted;

* indicates a stereoselective centre, and

R⁴ is selected from among:

PCT/EP01/10626

WO 02/22569

C₁₋₁₀ alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; C₃₋₈ cycloalkyl, saturated or unsaturated, unsubstituted or mono- or polysubstituted; aryl or heteroaryl, in each case unsubstituted or mono- or polysubstituted; or aryl, C₃₋₈ cycloalkyl or heteroaryl, in each case unsubstituted or mono- or polysubstituted, attached via saturated or unsaturated C₁₋₃ alkyl;

in the form of the racemates, enantiomers, diastereomers thereof, in particular mixtures of the enantiomers or diastereomers thereof or of a single enantiomer or diastereomer; in the form of their physiologically acceptable acidic and basic salts or salts with cations or bases or with anions or acids or in the form of the free acids or bases.

The term salt should be taken to mean any form of the active substance according to the invention, in which the latter assumes ionic form or bears a charge and is coupled with a counterion (a cation or anion) or is in solution. These should also be taken to mean complexes of the active substance with other molecules and ions, in particular complexes which are complexed by means of ionic interactions.

For the purposes of the present invention, a physiologically acceptable salt with cations or bases is taken to mean salts of at least one of the compounds according to the invention, usually a (deprotonated) acid, as the anion with at least one, preferably inorganic, cation, which is physiologically acceptable, in particular for use in humans and/or mammals. Particularly preferred

PCT/EP01/10626

WO 02/22569

salts are those of the alkali and alkaline earth metals, as are those with NH_4^+ , most particularly (mono-) or (di-) sodium, (mono-) or (di-)potassium, magnesium or calcium salts.

5

For the purposes of the present invention, a physiologically acceptable salt with anions or acids is taken to mean salts of at least one of the compounds according to the invention, usually protonated, for example
10 on the nitrogen, as the cation with at least one anion, which is physiologically acceptable, in particular for use in humans and/or mammals. In particular, for the purposes of the present invention, the physiologically acceptable salt is taken to be the salt formed with a physiologically
15 acceptable acid, namely salts of the particular active substance with inorganic or organic acids which are physiologically acceptable, in particular for use in humans and/or mammals. Examples of physiologically acceptable salts of certain acids are salts of: hydrochloric acid,
20 hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, 1,1-dioxo-1,2-dihydro-1,6-benzo[d]isothiazol-3-one (saccharinic acid),
25 monomethylsebacic acid, 5-oxo-proline, hexane-1-sulfonic acid, nicotinic acid, 2-, 3- or 4-aminobenzoic acid, 2,4,6-trimethylbenzoic acid, α -lipoic acid, acetylglycine, acetylsalicylic acid, hippuric acid and/or aspartic acid. The hydrochloride salt is particularly preferred.

30

In a preferred form of the compounds according to the invention, R^1 means C_{1-6} alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted, and R^2 means C_{2-9} alkyl, saturated or

PCT/EP01/10626

WO 02/22569

unsaturated, branched or unbranched, mono- or
polysubstituted or unsubstituted,

preferably

5

R^1 means C_{1-2} alkyl, mono- or polysubstituted or
unsubstituted, in particular methyl or ethyl and R^2
means C_{2-9} alkyl, preferably C_{2-7} alkyl, saturated or
unsaturated, branched or unbranched, mono- or
10 polysubstituted or unsubstituted, in particular ethyl,
propyl, n-propyl, i-propyl, butyl, n-butyl, i-butyl,
tert.-butyl, pentyl, hexyl or heptyl;

in particular

15

residue R^1 means methyl and R^2 means n-butyl.

In a preferred form of the compounds according to the
invention, R^3 is selected from among C_{1-3} alkyl, saturated or
20 unsaturated, branched or unbranched, mono- or
polysubstituted or unsubstituted, preferably methyl or
ethyl.

In a preferred form of the compounds according to the
25 invention, R^4 is selected from among C_{1-6} alkyl, saturated or
unsaturated, branched or unbranched, mono- or
polysubstituted or unsubstituted; phenyl or thiophenyl,
unsubstituted or monosubstituted (preferably with OCH_3 , CH_3 ,
OH, SH, CF_3 , F, Cl, Br or I); or phenyl attached via
30 saturated CH_2 , unsubstituted or monosubstituted (preferably
with OCH_3 , CH_3 , OH, SH, CF_3 , F, Cl, Br or I);

R^4 is preferably selected from among C_{1-6} alkyl,
saturated, unbranched and unsubstituted, in particular

PCT/EP01/10626

WO 02/22569

5 methyl, ethyl, propyl, n-propyl, i-propyl, butyl, n-butyl, i-butyl, *tert.*-butyl, pentyl or hexyl; phenyl or thiophenyl, unsubstituted or monosubstituted (preferably with OCH₃, CH₃, OH, SH, CF₃, F, Cl, Br or I); or phenyl attached via saturated CH₂, unsubstituted or monosubstituted (preferably with OCH₃, CH₃, OH, SH, CF₃, F, Cl, Br or I),

10 in particular R⁴ is selected from among methyl, ethyl or benzyl, unsubstituted or monosubstituted (preferably with OCH₃, CH₃, OH, SH, CF₃, F, Cl, Br or I).

15 In a preferred form of the compounds according to the invention, the compound is selected from among

- 3-ethylsulfanyl-2-formylamino-3-methyloctanoic acid ethyl ester or
 - 3-benzylsulfanyl-2-formylamino-3-methyloctanoic acid ethyl ester.
- 20

The compounds according to the invention are pharmacologically active, in particular as analgesics, and toxicologically safe, such that the invention also provides
25 pharmaceutical preparations containing the compounds according to the invention optionally together with suitable additives and/or auxiliary substances and/or optionally further active substances. The invention furthermore provides the use of the compounds according to
30 the invention for the production of a pharmaceutical preparation for the treatment of pain, in particular of neuropathic, chronic or acute pain, of epilepsy and/or migraine, together with corresponding treatment methods.

PCT/EP01/10626

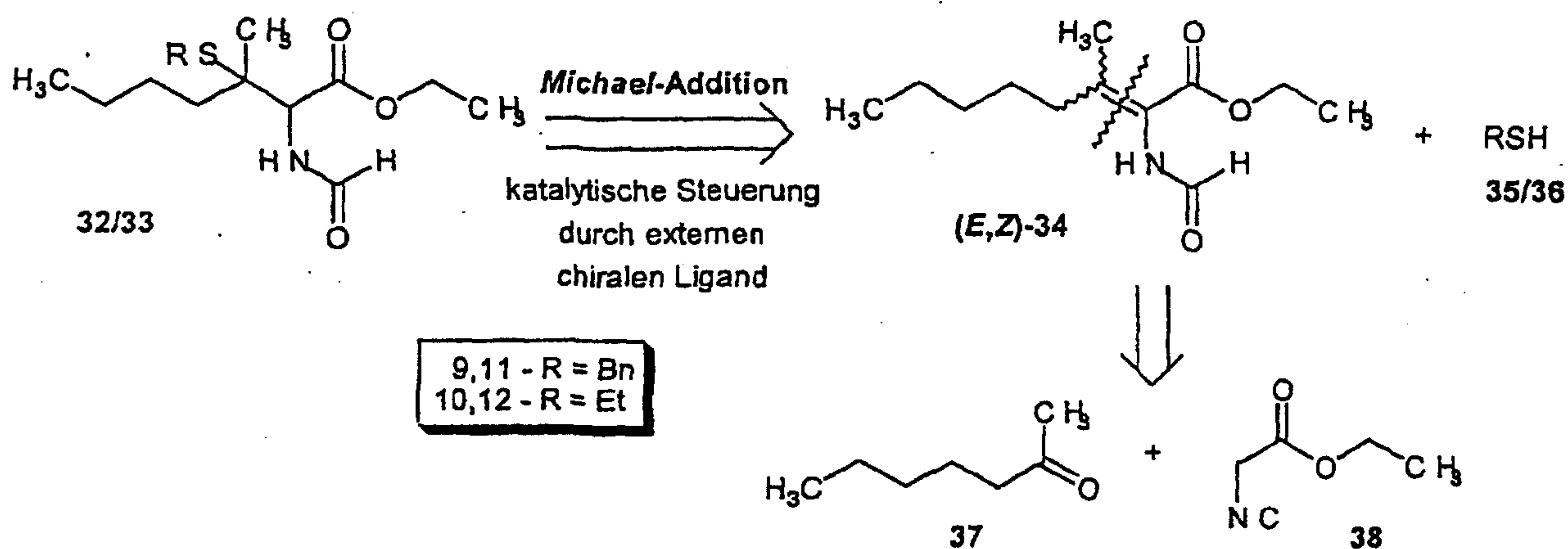
WO 02/22569

The following Examples are intended to illustrate the invention, but without restricting its scope.

Examples:**Example 1:****Synthetic pathway**

5

The target molecule 32/33 is to be prepared by a *Michael* addition. Figure 14 shows the retrosynthetic analysis of the educt 34 required for this approach:



- 10 **Figure 14: Retrosynthetic representation of the educt 34 for S-analogous *Michael* addition, wherein R denotes benzyl in the compounds 32 and 35 and ethyl in the compounds 33 and 36.**

15 Key: katalytische Steuerung durch externen chiralen Ligand = catalytic control by external chiral ligand

The 2-formylaminoacrylic acid ester 34 is to be produced in an olefination reaction from the ketone 37 and from isocyanoacetic acid ethyl ester (38).

20

Figure 15 shows the synthetic pathway for the preparation of 38:

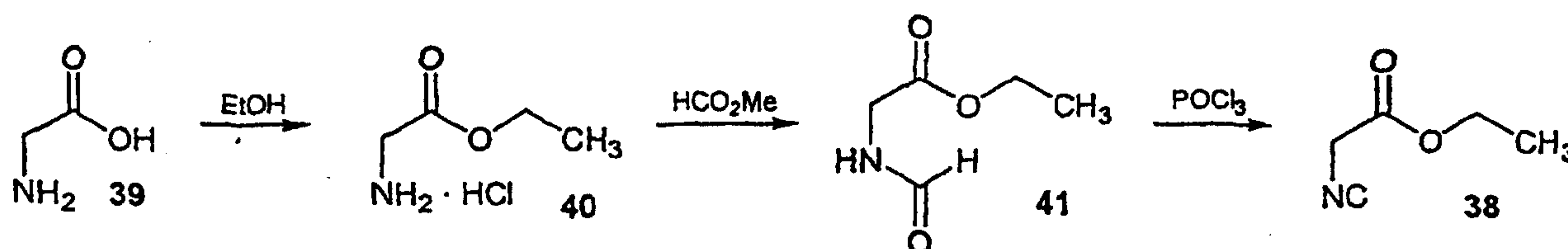


Figure 15: Planned synthesis for the preparation of the isocyanic ester **38**.

- 5 In the planned synthesis of **38**, glycine (**39**) is to be esterified in the first step with ethanol to yield the glycine ethyl ester (**40**). This latter compound is to be formylated on the amino function with methyl formate to form the formylamino ester **41**. The formylamino function of
- 10 the resultant 2-formylaminoacetic acid ethyl ester (**41**) is to be converted into the isocyano function with phosphoryl chloride to form the isocyanoacetic acid ethyl ester (**38**).

Example 2:

- 15 **Preparation of the chiral auxiliary reagent: (S,S)-1,2-dimethoxy-1,2-diphenylethane**

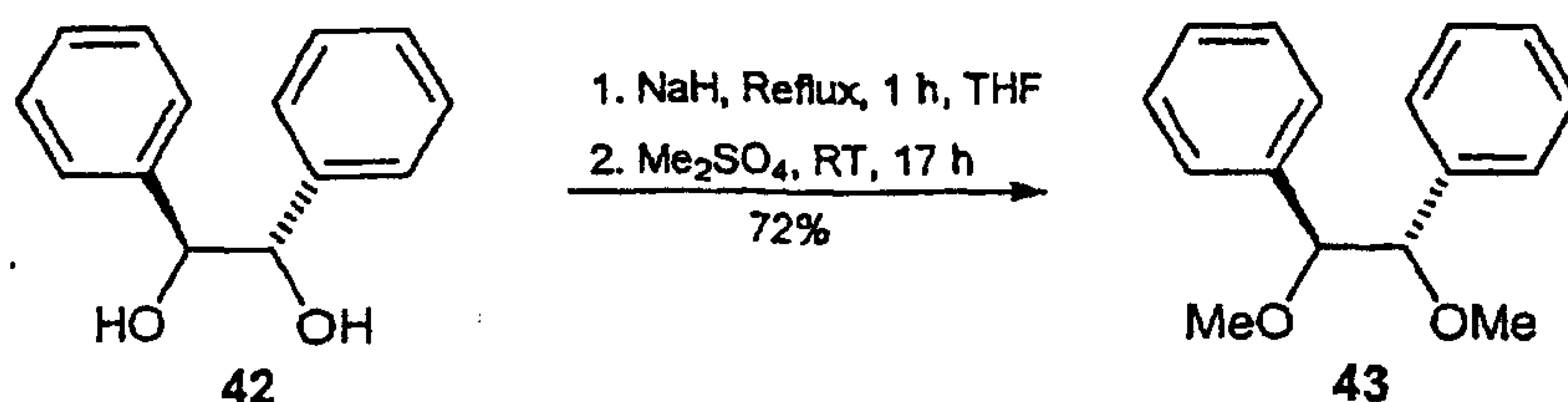


Figure 16: Production of the chiral dimethyl ether **43**.

- 20 The chiral dimethyl ether **43** was prepared in accordance with a method of K. Tomioka et al, (see Figure 16)^[34]. In this process, purified NaH was initially introduced in excess in THF, (S,S)-hydrobenzoin **42** in THF was added at RT and briefly refluxed. The solution was cooled to 0°C and
- 25 dimethyl sulfate was added dropwise. After 30 minutes' stirring, the white, viscous mass was stirred for a further 16 h at RT. After working up and recrystallisation from

PCT/EP01/10626

WO 02/22569

pentane, (*S,S*)-1,2-dimethoxy-1,2-diphenylethane (**43**) was obtained in the form of colourless needles and at yields of 72%.

5 Example 3:

Preparation of isocyanoacetic acid ethyl ester

The starting compound for synthesis of the isocyanoacetic acid ethyl ester (**38**) was prepared in accordance with the synthetic pathway shown in Figure 17:

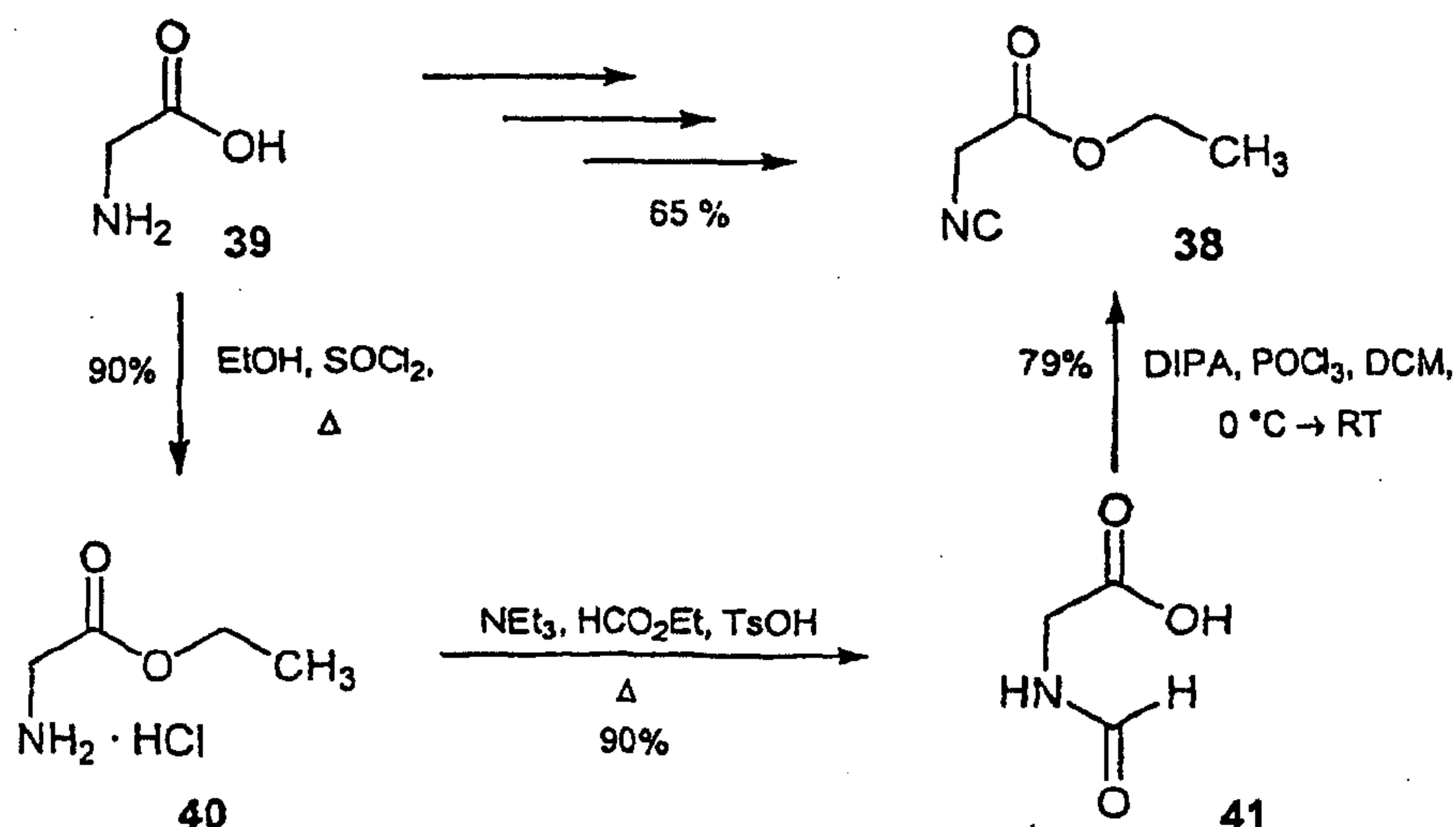


Figure 17: Synthetic route for isocyanoacetic acid ethyl ester (**38**).

15 Glycine (**39**) was here refluxed with thionyl chloride and ethanol, the latter simultaneously acting as solvent, for 2 hours. After removal of excess ethanol and thionyl chloride, the crude ester was left behind as a solid. After recrystallisation from ethanol, the glycine ethyl ester was
20 obtained as the hydrochloride (**40**) in yields of 90-97% in the form of a colourless, acicular solid.

The glycine ethyl ester hydrochloride (**40**) was formylated on the amino function in accordance with a slightly
25 modified synthesis after C.-H. Wong et al.^[35]. The glycine

PCT/EP01/10626

WO 02/22569

ester hydrochloride 40 was here suspended in methyl formate and toluenesulfonic acid was added thereto in catalytic quantities. The mixture was refluxed. Triethylamine was then added dropwise and refluxing of the reaction mixture
5 was continued. Once the reaction mixture had cooled, the precipitated ammonium chloride salt was filtered out. Any remaining ethyl formate and triethylamine were stripped out from the filtrate and the crude ester was obtained as an orange oil. After distillation, the 2-formylaminoacetic
10 acid ethyl ester (41) was obtained as a colourless liquid in yields of 73-90%.

The formylamino group was converted into the isocyano group in accordance with a method of *I. Ugi et al.*^[36]. The formylaminoacetic acid ethyl ester (41) was introduced into
15 diisopropylamine and dichloromethane and combined with phosphoryl chloride with cooling. Once addition was complete, the temperature was raised to RT and the reaction mixture was then hydrolysed with 20% sodium hydrogen carbonate solution. After working up and distillative
20 purification, the isocyanoacetic acid ethyl ester (38) was obtained in yields of 73-79% as a light yellow, photosensitive oil.

Using phosphoryl chloride made it possible to avoid the handling difficulties associated with phosgene. In so doing
25 in this stage, a reduction in yield of approx. 10% according to the literature^{[37], [38]} was accepted.

An overall yield of 65% was achieved over three stages, it being straightforwardly possible to perform the first two stages in large batches of up to two moles. In contrast,
30 due to the large quantity of solvent and the elevated reactivity of phosphoryl chloride, the final stage could only be performed in smaller batches of up to 0.5 mol.

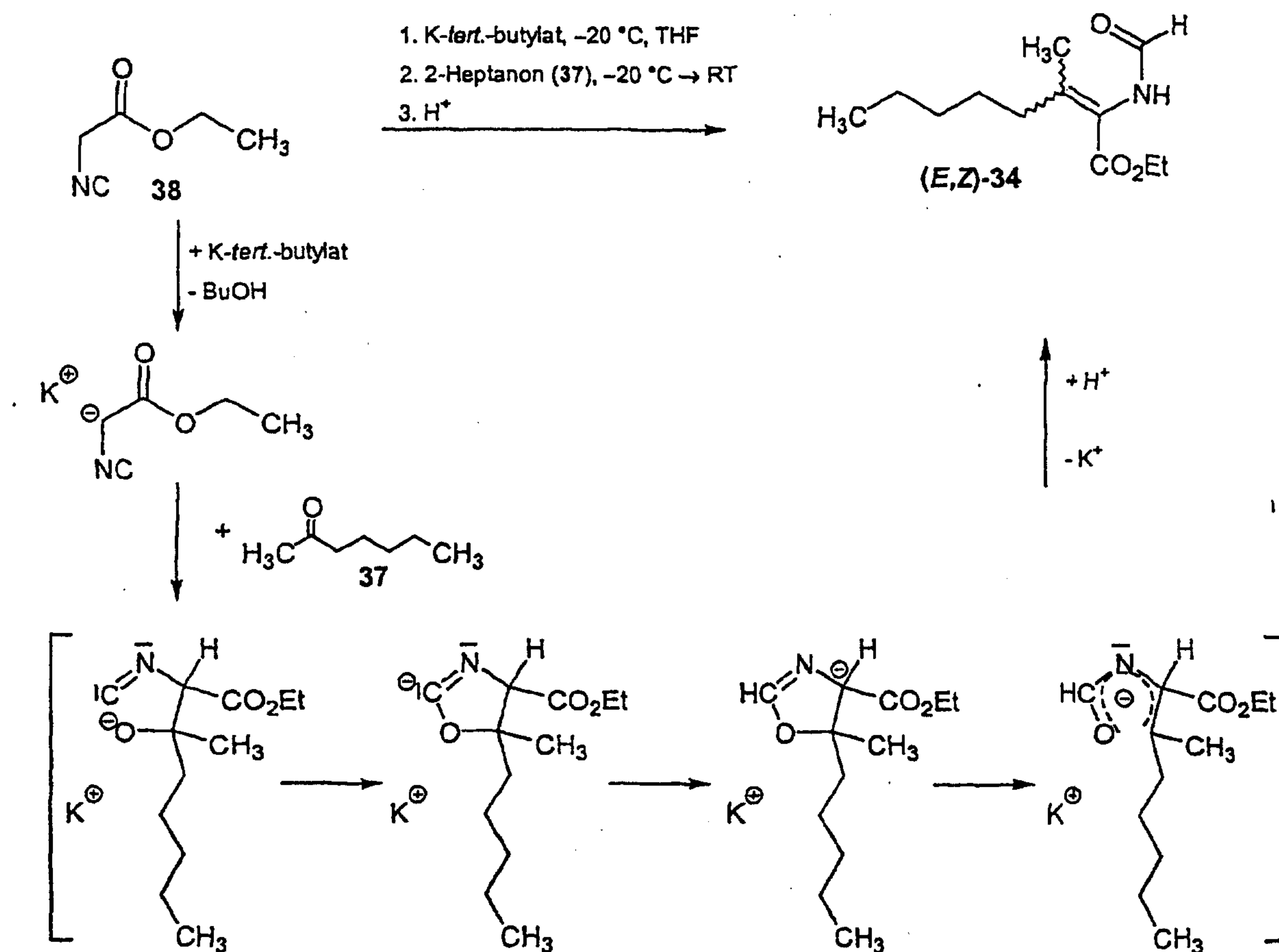
Example 4:**Preparation of (E)- and (Z)-2-formylamino-3-methyl-2-octenoic acid ethyl ester**

- 5 The (E)- and (Z)-2-formylamino-3-methyl-2-octenoic acid ethyl esters (34) were prepared in accordance with a method after U. Schöllkopf et al.^{[39],[40]}. The isocyanoacetic acid ethyl ester (38) was deprotonated in α position *in situ* at low temperatures with potassium tert.-butanolate. A
- 10 solution of 2-heptanone (37) in THF was then added dropwise. After 30 minutes' stirring, the temperature was raised to room temperature. The reaction was terminated by the addition of equivalent quantities of glacial acetic acid.
- 15 The 2-formylamino-3-methyl-2-octenoic acid ethyl ester (34) was still in the form of (E/Z) mixtures, wherein these could readily be separated by chromatography. The overall yields of the purified and separated (E) and (Z) isomers amounted to 73% in the form of colourless solids.

20

- In this reaction, which Schöllkopf^[41] termed "formylaminomethylenation of carbonyl compounds", the oxygen of the ketone is replaced by the (formylamino-alkoxycarbonyl-methylene) group and the β -substituted α -
- 25 formylaminoacrylic acid ester 34 is directly formed in a single operation. According to Schöllkopf, the reaction is based on the mechanism shown in Figure 18^[42].

Figure 18: Mechanism of "formylaminomethylenation of carbonyl compounds" after *Schöllkopf*^[42].



Key: K-*tert.*-butylat = K *tert.*-butylate ; 2-Heptanon = 2-heptanone

5 In this reaction, the isocyanoacetic acid ethyl ester **38** is first deprotonated in α position with potassium *tert.*-butylate. The carbanion then subjects the carbonyl C atom on the ketone **37** to nucleophilic attack. After several
10 intramolecular rearrangements of the negative charge and subsequent protonation, the β -substituted α -formylaminoacrylic acid esters **34** are obtained. Since the 2-formylamino-3-methyl-2-octenoic acid ethyl esters (**34**) are always obtained in (E/Z) mixtures, the
15 question arose of the possible influence of temperature on the (E/Z) ratio.

PCT/EP01/10626

WO 02/22569

Table 4: Influence of reaction temperature on the (E/Z) ratio.

Reaction temperature	(E/Z) ratio ^[a]
0°C → RT	57:43
-40°C → RT	63:37
-78°C → RT	62:38

^[a] determined by ¹³C-NMR

5

Table 4 shows the influence of temperature on (E/Z) ratios. The reactions were performed under the above-described conditions. Only the initial temperatures were varied. It can be seen that temperature had only a slight influence on the (E/Z) ratios. However, since both isomers are required for the synthesis, the balanced ratio at approx. 0°C is advantageous since both isomers could be obtained in approximately equal quantities by chromatography. (E/Z) assignment was carried out after U. Schöllkopf^[39], in accordance with which the protons of the methyl group in β position of the (Z) isomer absorb at a higher field than do those of the (E) isomer^[43].

20 **Example 5:****Michael addition with thiols as donor****A) Tests with thiolates as catalyst**

Since the Michael addition of thiols onto 2-formylamino-3-methyl-2-octenoic acid ethyl ester (**34**) does not proceed without a catalyst, a method after T. Naito et al.^[44] was initially used. In this method, a mixture of thiol and lithium thiolate was first produced in a 10:1 ratio, before the 2-formylaminoacrylic acid ethyl ester **34** was added.

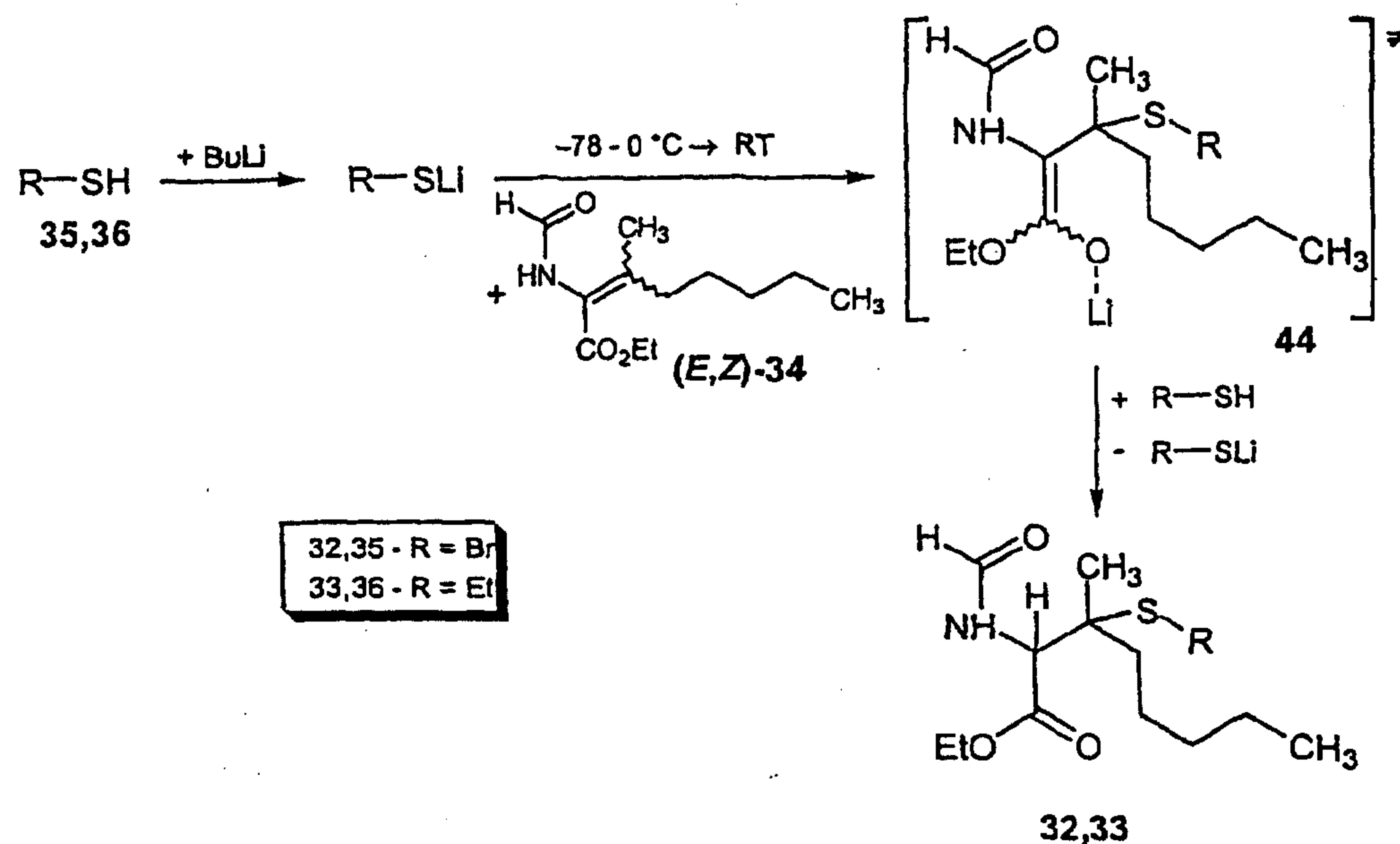


Figure 19: Mechanism of thiolate-catalysed *Michael* addition^[44].

5 The reaction is assumed to be based on the mechanism shown in Figure 19^[44]. After addition of the thiolates **35** or **36** onto the 2-formylamino-3-methyl-2-octenoic acid ethyl ester [**(E,Z)-34**] in β position, this adduct **44** is directly
 10 forming the *Michael* adduct **32**, **33**.

The *Michael* adducts **32**, **33** were prepared by initially introducing 0.1 equivalents of BuLi in THF and adding 10 equivalents of thiol at 0°C. The **(E)-** or **(Z)-34** dissolved in THF was then added dropwise at low temperature and the
 15 mixture was slowly raised to RT.

After hydrolysis with 5% NaOH and column chromatography, **32**, **33** were obtained as colourless, viscous oils, in the form of diastereomer mixtures.

Table 5 lists the *Michael* adducts prepared in accordance
 20 with the described synthesis:

Table 5: Prepared Michael adducts.

Educt	Thiol	T [°C]	Product	dr ^[a]	de [%] ^[a]	Yield
<u>(Z)-34</u>	<u>35</u>	-78°C → RT	<u>32</u>	58:42	16	83%
<u>(Z)-34</u>	<u>35</u>	-25°C → -15°C	<u>32</u>	59:41	18	98%
<u>(E)-34</u>	<u>35</u>	-78°C → RT	<u>32</u>	41:59	18	79%
<u>(Z)-34</u>	<u>36</u>	-78°C → RT	<u>33</u>	57:43	14	82%

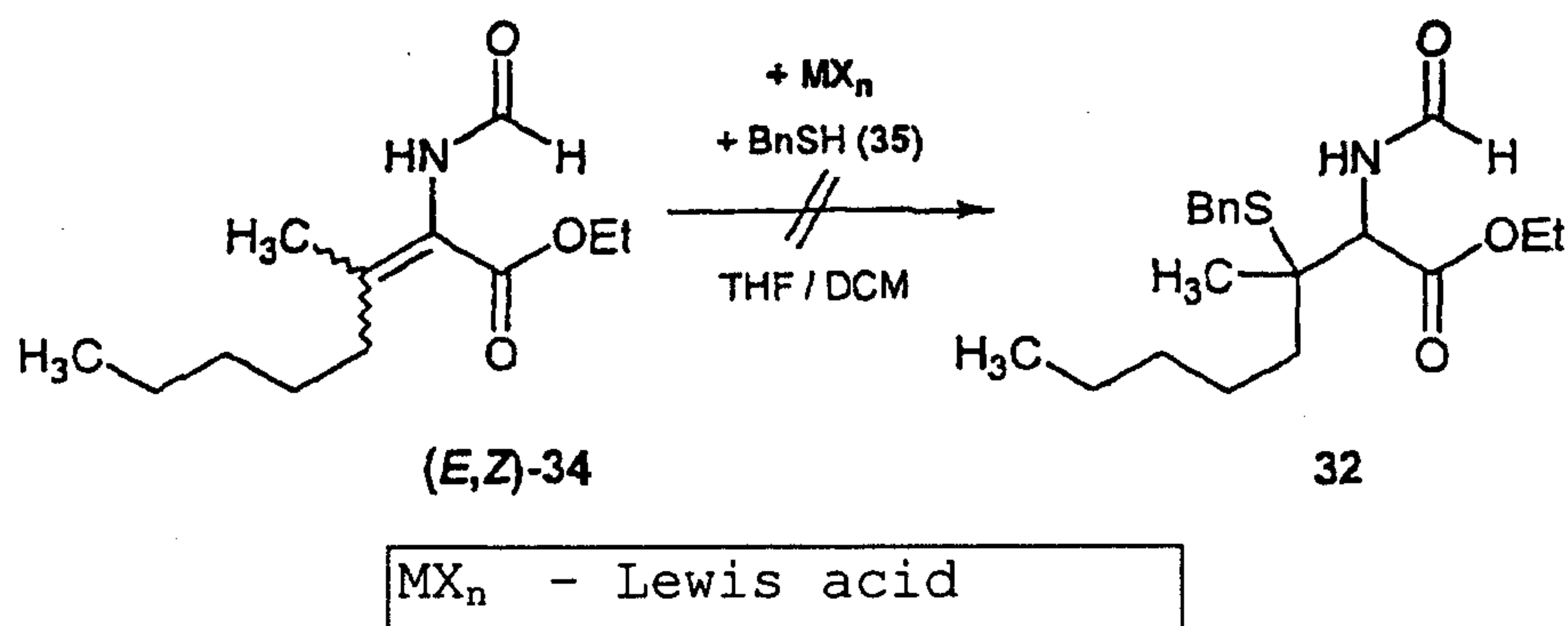
^[a] determined by ¹³C-NMR after chromatography

5 As can be seen from Table 5, while selection of the formylamino-3-methyl-2-octenoic acid ethyl ester does predetermine (Z)-34 or (E)-34, only the preferential diastereoisomer was determined as a consequence. It was not possible in THF to achieve better predetermination with de
10 values of >18%, as the reaction only starts in this medium at ≥ -20°C and better control is not to be anticipated at higher temperatures.

The *threo*/*erythro* diastereomers 32 could initially be separated from one another by preparative HPLC. As a
15 result, it was found that the *threo* diastereomer (threo)-32 was a solid, while the *erythro* diastereomer (erythro)-32 was a viscous liquid.

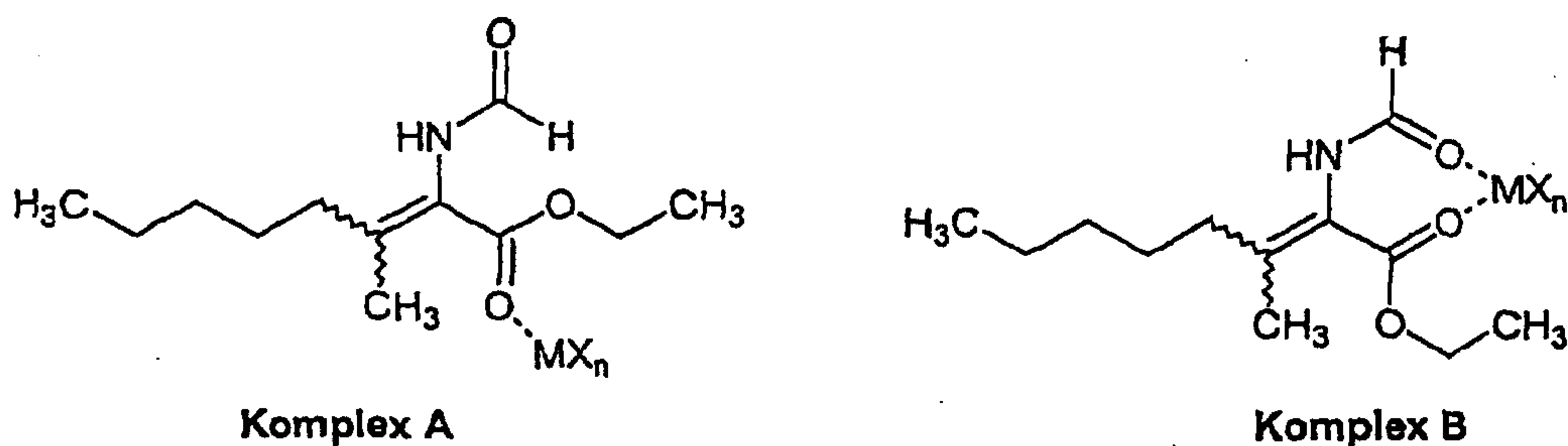
The attempt was thus made to separate the *threo*/*erythro* diastereomers 32 from one another by crystallisation. The
20 diastereomer mixtures 32 were dissolved in the smallest possible quantities of pentane/ethanol (~10:1) and cooled to -22°C for a period of at least 5 d, during which the diastereomer (threo)-32 crystallised out as a solid. In this manner the enriched diastereomers (threo)-32 and
25 (erythro)-32 were obtained with diastereomeric excesses of 85-96% for (threo)-32 and of 62-83% for (erythro)-32.

B) Tests with Lewis acids as catalyst

Figure 20: Lewis acid-catalysed *Michael* addition.

5

As can be seen in Figure 20, the attempt was made to catalyse the *Michael* addition of benzyl mercaptan onto 2-formylaminoacrylic acid ethyl ester 34 by adding a Lewis acid MX_n . There are many examples of the activation of α,β -unsaturated esters by various Lewis acids for the addition of thiols ^[27]. In this case, one of the postulated complexes **A** or **B** would be formed in which the metal is coordinated on the carbonyl oxygen (see Figure 21).



15 Figure 21: Postulated Lewis acid complexes.

Key: Komplex = complex

The double bond should be so strongly activated by this complex that the reaction proceeds directly.

20 The Lewis acids MX_n listed in Table 6 were tested in various solvents for their catalytic action on this *Michael* reaction. In these tests, one equivalent of the 2-formylamino-3-methyl-2-octenoic acid ethyl ester (34) were initially introduced in THF or DCM and one equivalent of

the dissolved or suspended Lewis acid was added at 0°C. 1.2 equivalents of benzyl mercaptan were then added dropwise and the mixture raised to room temperature after 2 h. Some of the batches were also refluxed, if there was no discernible reaction after one day.

Table 6: Tested Lewis acids for catalysis of *Michael* addition.

Lewis acid MX_n	Solvent	Tempera- ture T	Conversion^[a]
TiCl ₄	DCM	RT	no conversion after 18 h
Ti(O- <i>i</i> -Pr) ₃ Cl	THF	RT	no conversion after 18 h
YbTf ₃	DCM	RT	no conversion after 3 d
YbTf ₃	THF	1 d RT + 1 d reflux	no conversion after 2 d
YCl ₃	DCM	RT	no conversion after 3 d
SnTf ₂	DCM	RT	no conversion after 3 d
ZnTf ₂	DCM	RT	no conversion after 3 d
ZnCl ₂	THF	RT	no conversion after 4 d
SnCl ₄	DCM	1 d RT + 1 d reflux	no conversion after 2 d
SnCl ₄	THF	1 d RT + 1 d reflux	no conversion after 2 d
BF ₃ ·EtO ₂	DCM	RT	no conversion after 2 d
AlCl ₃	THF	RT	no conversion after 2 d

^[a] determined by TLC samples or by NMR

Only with TiCl₄ was there a colour change, which would indicate formation of a complex. In contrast, there was no colour change indicating the formation of a complex with any of the other Lewis acids. None of the tested Lewis acids exhibited any catalytic action, as there was no identifiable conversion in any of the cases after a

reaction time of up to 3 days and the educts could be recovered in their entirety.

C) Testing of catalysis with Lewis acids with the addition 5 of bases

The *Michael* addition of thiols onto α,β -unsaturated ketones may be catalysed as described in section 1.2.4 by the addition of bases (for example triethylamine) ^[45]. The
10 Brønsted base here increases the nucleophilic properties of the thiol to such a level that it is capable of initiating the reaction.

When reacting equimolar quantities of 2-formylamino-3-methyl-2-octenoic acid ethyl ester (**34**), benzyl mercaptan
15 (**35**) and triethylamine in THF, no catalytic action could be observed at reaction temperatures of up to 60°C. The starting materials could be recovered.

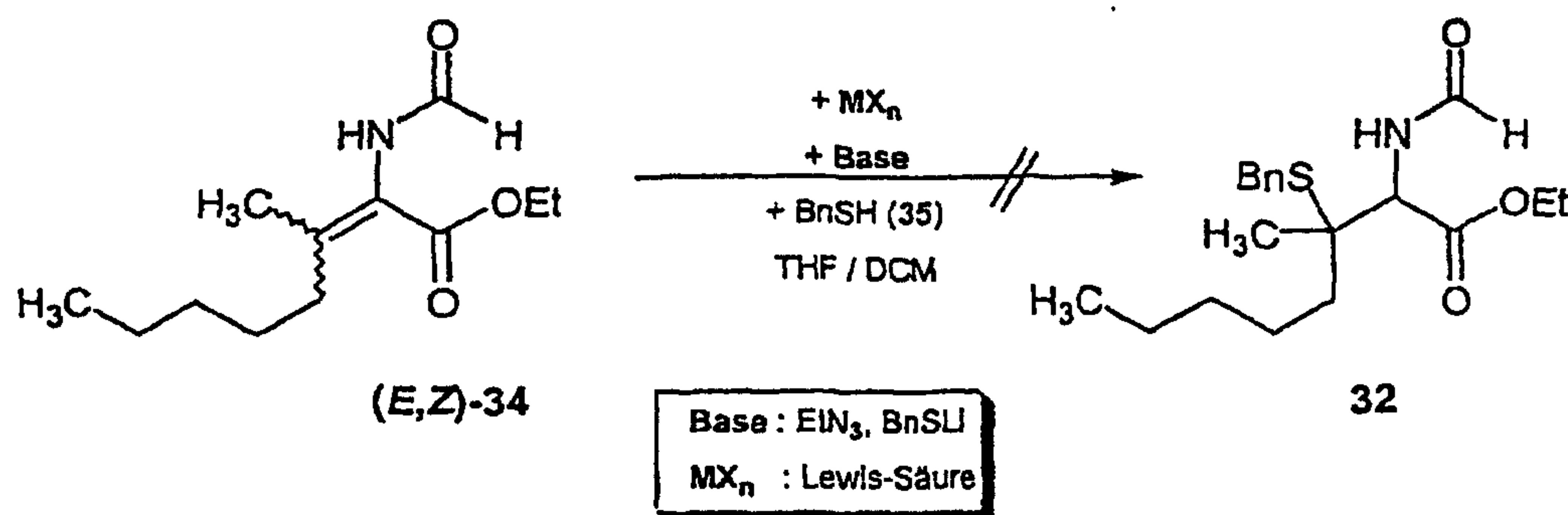


Figure 22: Catalysis by base and Lewis acid.

20 Key: Lewis-Säure = Lewis acid

The idea of combining Lewis acid catalysis (presented in section 2.6.2) with base catalysis (see Figure 22), thus arose because catalysis did not work with Lewis acids or
25 Brønsted bases alone.

In the combinations of bases and Lewis acids shown in Table 7, one equivalent of 2-formylamino-3-methyl-2-octenoic acid ethyl ester (**34**) was initially introduced in

the stated solvent and a solution prepared from 1.2 equivalents of benzyl mercaptan (**35**) and 1 equivalent of the stated base was added dropwise at 0°C. After 2 h the mixture was raised to room temperature and stirred for a further 3 days. There was no discernible conversion with any of the combinations of bases and Lewis acids. Even in the batch in which benzyllithium thiolate was used as the base in combination with TiCl₄, there was no observable conversion, although without the addition of TiCl₄ complete conversion could be achieved even at 0°C.

Table 7: Tested combinations of bases and Lewis acids for catalysis of *Michael* addition.

Lewis acid	Base	Solvent	Conversion ^[a]
-	NEt ₃	THF	-
TiCl ₄	NEt ₃	THF	-
TiCl ₄	BnSLi	THF	-
TiCl ₄	BnSLi	THF	+
TiCl ₄	NEt ₃	DCM	-
AlCl ₃	NEt ₃	THF	-

^[a] determined by TLC samples

D) Influence of the solvent

The question then arose of identifying the suitable solvent in order possibly to achieve higher *de* values under reaction conditions as described in section 2.6.1 by varying the solvent.

Table 8: Influence of solvent on the addition of benzyl mercaptan (35) onto (E,Z)-34.

Educt	Solvent	Temperature	Reaction time	dr ^[a]	de [%] ^[a]
<u>(Z)-34</u>	THF	-20°C → -15°C	2h	59:41	18
<u>(E)-34</u>	THF	-78°C → RT	2h	41:59	18
<u>(Z)-34</u>	Ether	-25°C → -5°C	2h	63:27	26
<u>(Z)-34</u>	Toluene	0°C → RT	18h	72:28	44
<u>(E)-34</u>	Toluene	0°C → RT	18h	32:68	36
<u>(Z)-34</u>	DCM	0°C → RT	7d-17d ^[b]	75:25	50
<u>(E)-34</u>	DCM	0°C → RT	7d-17d ^[b]	25:75	50

^[a] determined by ¹³C-NMR after chromatography

5 ^[b] only approx. 50% conversion

As can be seen from Table 8, the de value could be raised by selecting other solvents. A distinct rise was evident with the nonpolar solvents such as toluene and DCM. In this case, de values of 50% were achieved, but the reaction time increased from 2 h in THF to 17 d in DCM. Moreover, with DCM, conversion of only 50% was observable after 7-17 d.

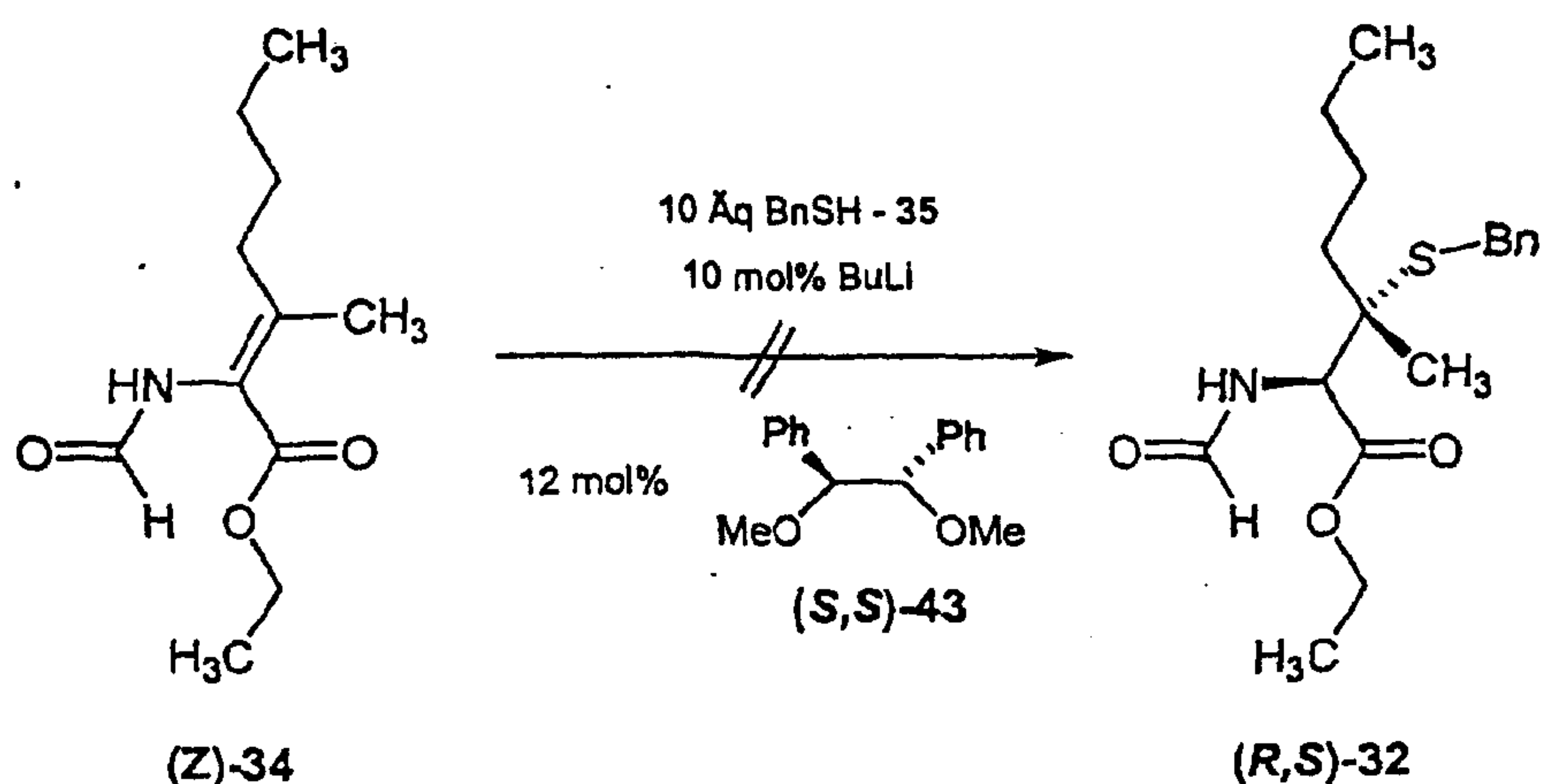
E) Tests of control by complexation of the Michael donor

Figure 23: Michael addition with control by chiral diether **(S,S)-43**.

5 Key: Äq = eq.

The aim was to control the Michael reaction by the addition of a chiral compound to the thiolate-catalysed reaction (see section 2.6.1) (see Figure 23).

10 Control was achieved according to Tomioka et al.^[33] by chiral bi- or triethers. The benzyllithium thiolate was used in this case in only catalytic quantities. Addition of the chiral dimethyl ether **(S,S)-43** was intended to complex the lithium thiolate, in order to control the attack
15 thereof. Instead of the diastereomer mixture produced according to sections 2.5.1 and 2.5.4, the intention was to form only one diastereomer enantioselectively.

It is assumed that the chelate shown in Figure 24 is formed^[32]. In this chelate, the lithium thiolate is
20 complexed by both the oxygen atoms of the dimethyl ether. On attack, the carbonyl oxygen of the Michael acceptor **34** also coordinates on the central lithium atom, so controlling the reaction.

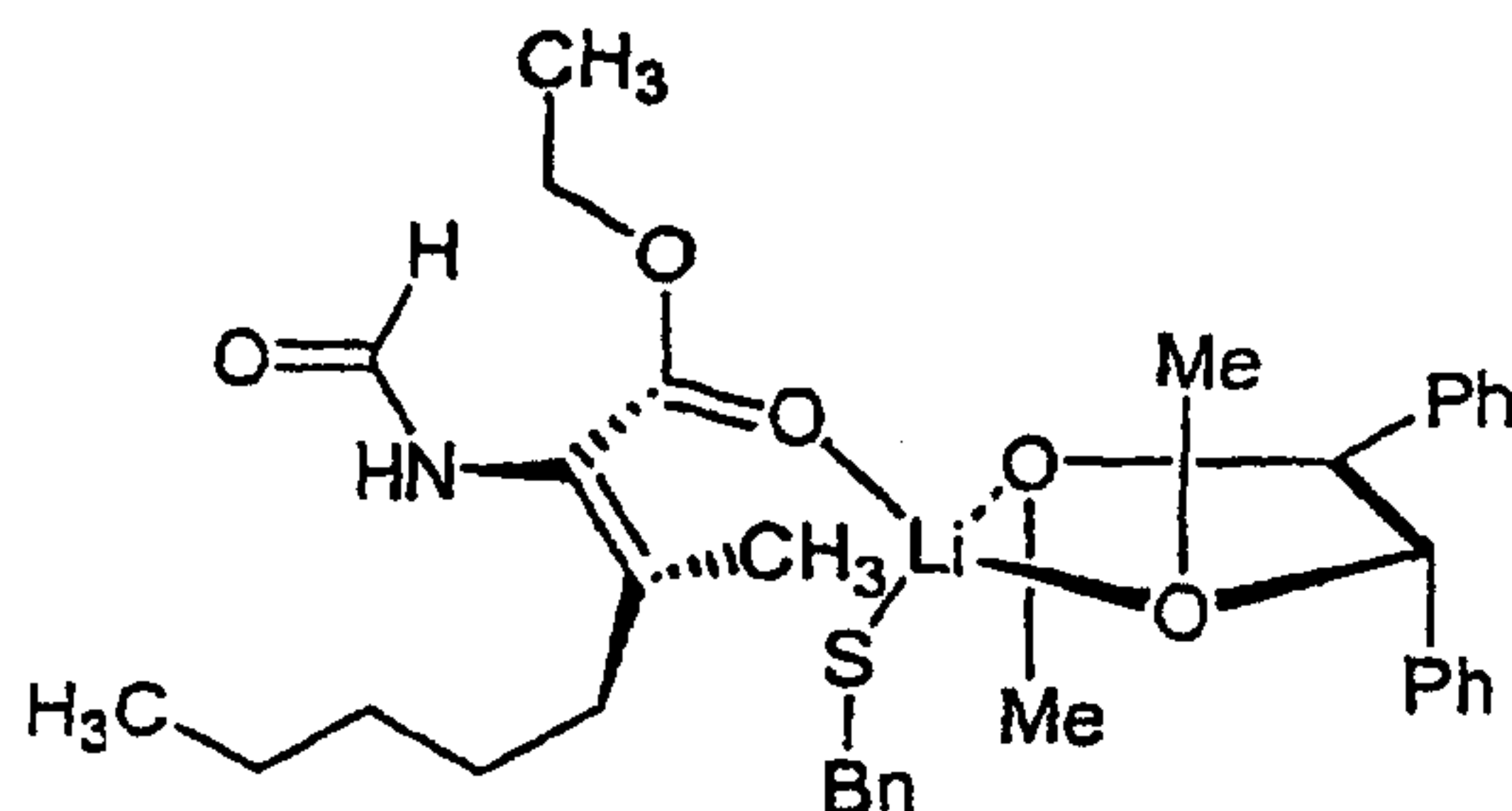


Figure 24: Postulated complex for controlling *Michael* addition, by addition of the dimethyl ether (S,S)-43.

5 **Table 9:** Tests of control with the chiral dimethyl ether (S,S)-43.

Educt	Solvent	Chiral diether <u>(S,S)-43</u>	Reaction time	<i>dr</i>^[a]	<i>ee</i> [%]^[b] of the diastereomers
<u>(Z)-34</u>	THF	—	2h	59:41	0
<u>(Z)-34</u>	Ether	0.12 eq	2h	63:37	5-7
<u>(Z)-34</u>	Toluene	0.12 eq	18h	71:29	4
<u>(Z)-34</u>	Toluene	—	18h	72:28	1-4
<u>(Z)-34</u>	DCM	0.12 eq	17d	75:25	1-9
<u>(Z)-34</u>	DCM	—	17d	79:21	4-6
<u>(E)-34</u>	Toluene	0.12 eq	18h	30:70	1
<u>(E)-34</u>	Toluene	—	18h	32:68	0
<u>(E)-34</u>	DCM	0.12 eq	7d	25:75	5-7
<u>(E)-34</u>	DCM	.	7d	32:68	1-6
<u>(E)-34</u>	THF	—	2h	41:59	0

^[a] by ¹³C-NMR spectroscopy after chromatography

^[b] according to HPLC_{anal}.

10

Testing of control by the dimethyl ether (S,S)-43 was performed in ether, DCM and toluene. 0.1 equivalents of BuLi were initially introduced at 0°C and 10 equivalents of benzyl mercaptan 35 were added. 0.12 equivalents of the dissolved dimethyl ether (S,S)-43 were added thereto.

15

PCT/EP01/10626

WO 02/22569

However, no colour change indicating the formation of a complex was to be seen. 30 min later, one equivalent of 2-formylamino-3-methyl-2-octenoic acid ethyl ester **34** was added dropwise at 0°C. The reaction was terminated after
5 the time stated in each case by the addition of 5% NaOH. The diastereomeric excesses were determined by chromatography from the ¹³C-NMR spectra after purification by column spectroscopy. The enantiomeric excesses were determined after crystallisation of the diastereomers
10 **(threo)-32** (pentane/ethanol) by analytical HPLC on a chiral stationary phase.

As can be seen from Table 9, no chiral induction of the *Michael* addition was discernible from the addition of the chiral dimethyl ether, as the measured enantiomeric
15 excesses are within the accuracy of the HPLC method. The reason for this is that the purified diastereomers are contaminated with the other diastereomer and it was not possible to measure all four isomers together with baseline separation.

20

Example 6

Summary

In the context of the present invention, a synthetic route
25 was first of all devised for the preparation of (E,Z)-2-formylaminoacrylic acid esters **(E,Z)-34**. This was achieved with a four stage synthesis starting from glycine (**39**). After esterification, N-formylation, condensation of the N-formylamino function and olefination **(E,Z)-34** was obtained
30 in an overall yield of 47% and with an (E/Z)-ratio of 1:1.3 (see Figure 25).

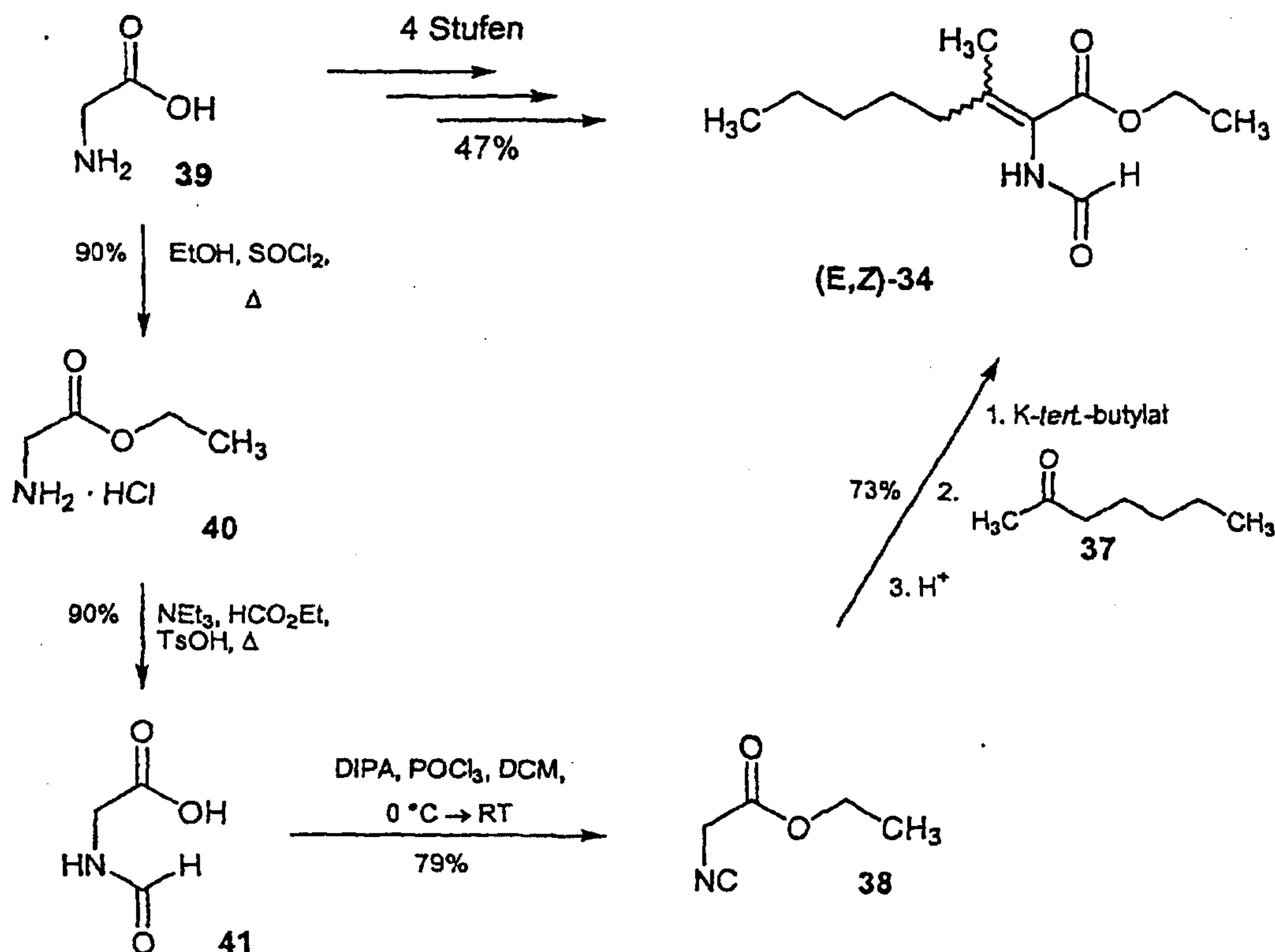


Figure 25: Synthesis of (E,Z)-2-formylaminoacrylic acid esters **(E,Z)-34**.

Key: 4 Stufen = 4 stages; K-tert.-butylat = K tert.-butoxide

5

It was intended to add mercaptans onto the synthesised (E,Z)-2-formylaminoacrylic acid esters **(E,Z)-34** in a Michael addition. The reaction could be catalysed by addition of 0.1 equivalents of lithium thiolate.

- 10 In order to enable enantioselective control by means of chiral catalysts, the use of various catalysts was investigated, which may subsequently be provided with chiral ligands. Lewis acids, Brønsted bases and a combination of the two were tested in various solvents for
- 15 their catalytic action (see Figure 26). However, no catalytic systems have yet been found for the desired Michael addition.

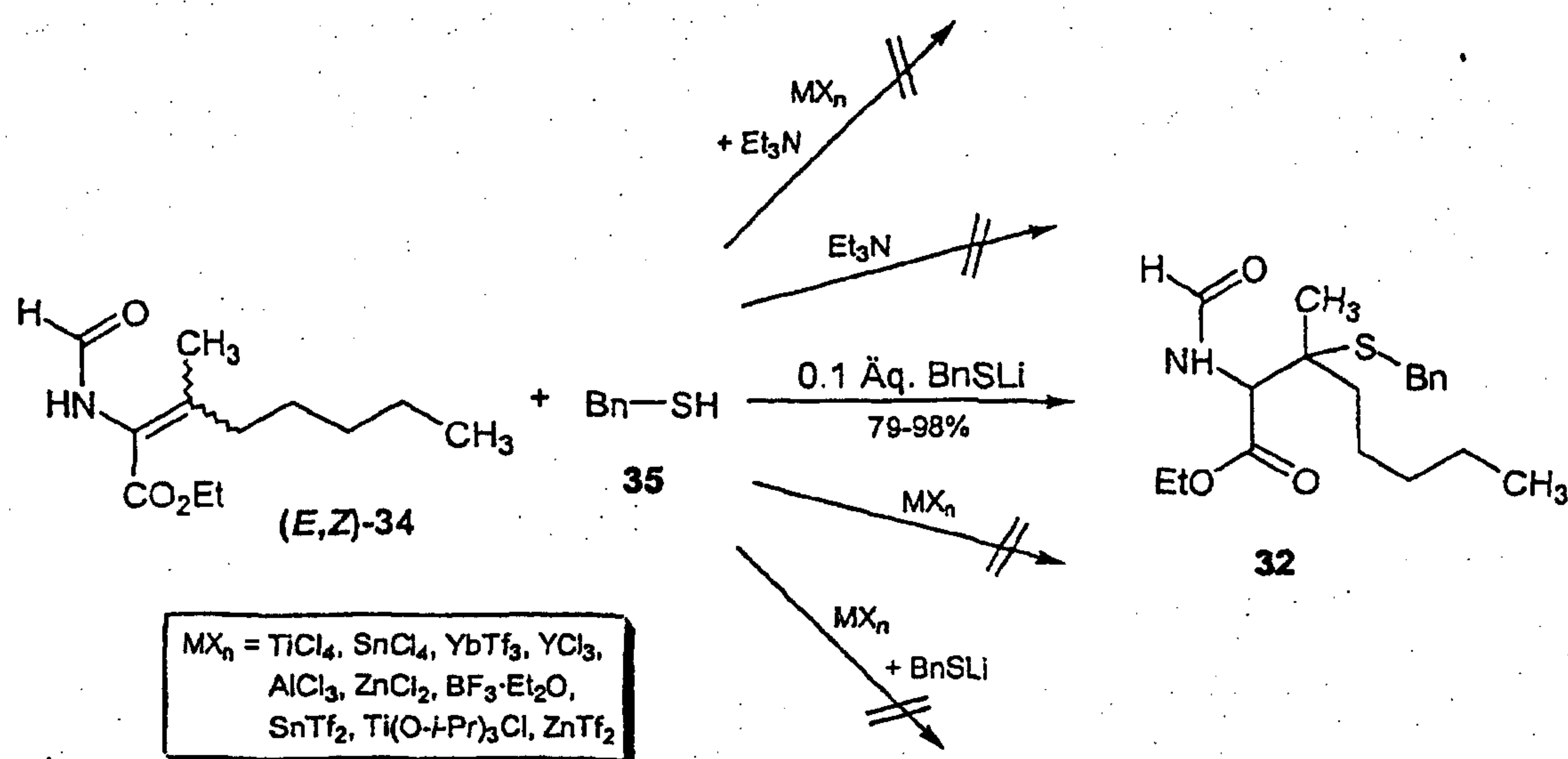


Figure 26: Tests for catalysis of S-analogous Michael addition.

Key: Äq = eq.

5

A mixture of both diastereomers was obtained from thiolate-catalysed Michael addition. By changing solvent, the diastereomeric excess when using **(Z)-34** could be raised from 17% (THF) to 43% (toluene) and 50% (DCM). Starting from **(E)-34**, comparable de values were achieved with the inverse diastereomeric ratio. However, as the de value increases, so too does the reaction time from 2 h (THF) to up to 17 d (DCM), in order to achieve satisfactory conversion.

15 By crystallising the threo diastereomer **(threo)-32** from pentane/ethanol (10:1), the threo and erythro diastereomers **32** could be further purified to a de value of 96% for **(threo)-32** and 83% for **(erythro)-32**.

On the basis of the successful catalysis with 0.1 equivalents of thiolate, the attempt was made to control the attack of thiolate by addition of the chiral diether (S,S)-1,2-dimethoxy-1,2-diphenylethane [**(S,S)-43**] ^[33].

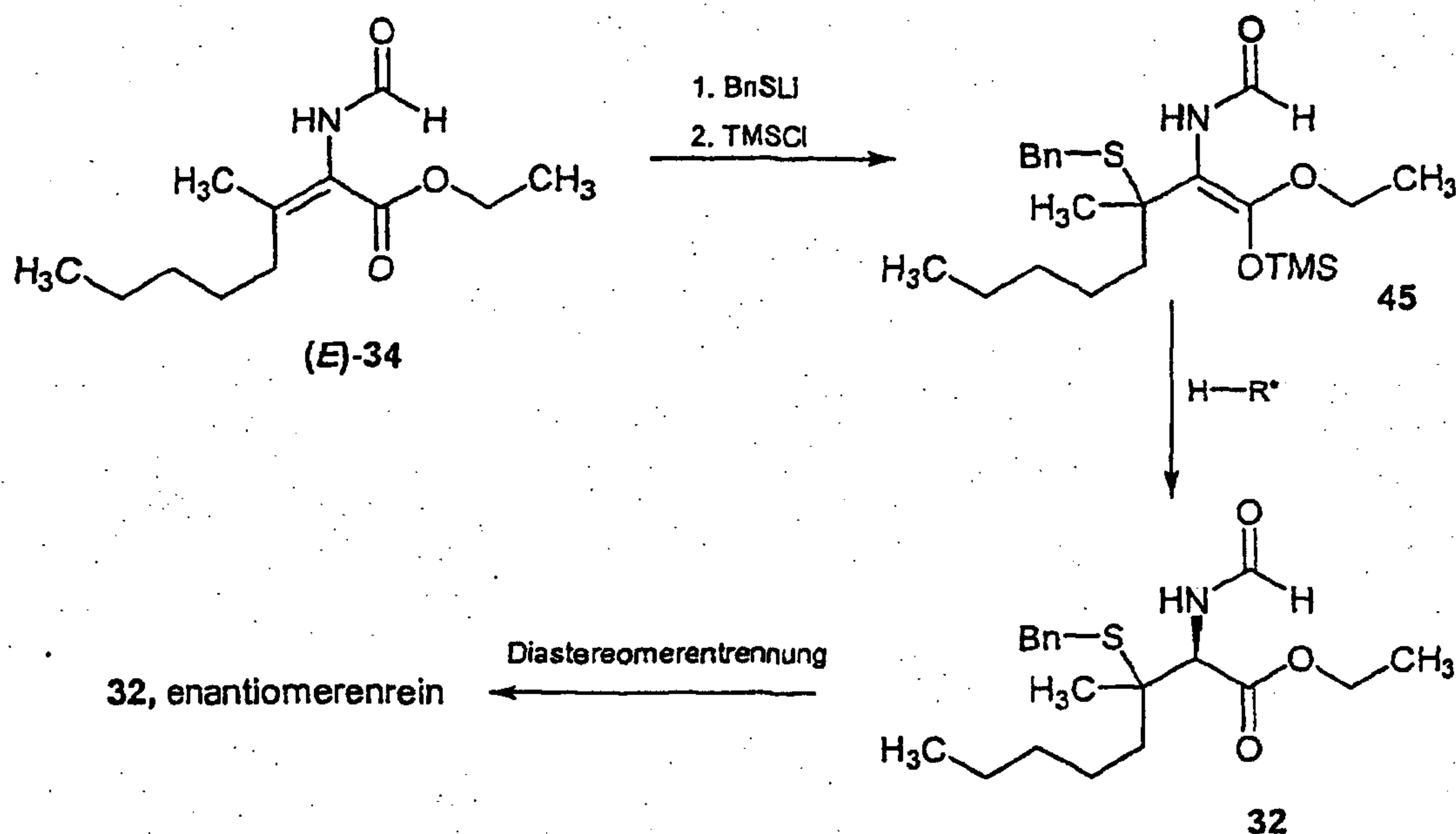
Nonpolar solvents were used for this purpose. However no

influence of the diether (S,S)-43 on the control of the reaction has yet been observable.

Example 7:

5 Use of TMSCl

Since the diastereomer separation developed in the present invention works well, the thiolate may be used stoichiometrically as shown in Example 5A and the adduct preferably scavenged with TMSCl as the enol ether 45. Protonating this adduct 45 with a chiral proton donor R^*-H makes it possible to control the second centre (see Figure 27).



15 **Figure 27:** Control of a centre with subsequent separation of the diastereomers.

Key: Diastereomerentrennung = separation of the diastereomers;
enantiomerenrein = enantiomerically pure.

20 The two enantiomerically pure diastereomers formed may, as described, be separated by crystallisation. This type of control makes all four stereoisomers individually accessible.

Example 8:**Use of sterically demanding groups:**

A second possibility for controlling Michael addition is intramolecular control by sterically demanding groups, preferably the TBDMS group. These may be introduced enantioselectively using a method of *D. Enders and B. Lohray* ^{[46], [47]}. The α -silyl ketone **47** produced starting from acetone (**46**) was then reacted with isocyanoacetic acid ethyl ester (**38**) to yield the 2-formylamino-3-methyl-4-(*t*-butyldimethylsilyl)-2-octenoic acid ethyl ester **(E)-48** and **(Z)-48** (see Figure 28).

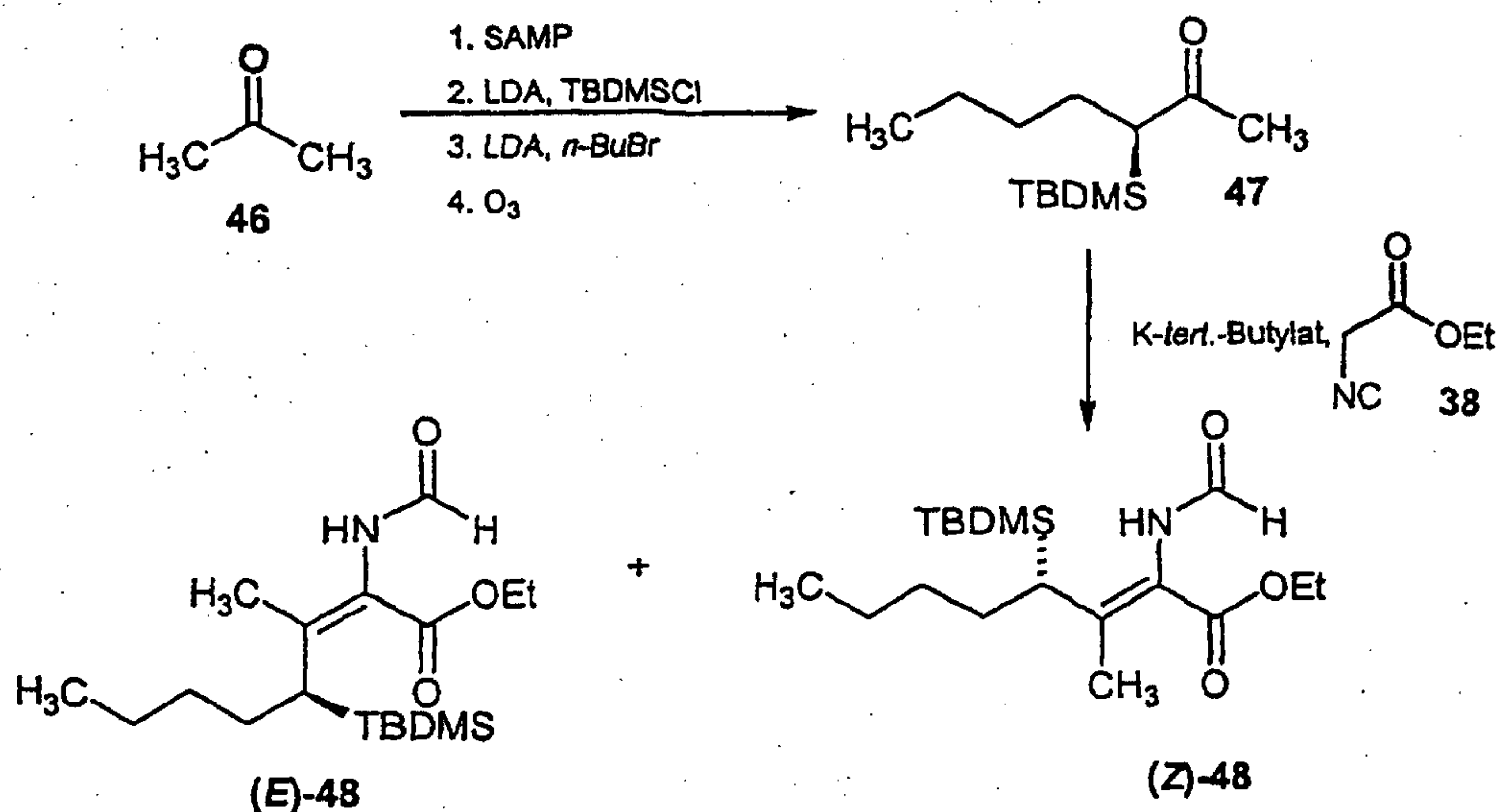


Figure 28: Introduction of the controlling TBDMS group.

Key: K-*tert.*-Butylat = K *tert.*-butylate

(E)-48 and **(Z)-48** are then reacted with a thiol in a Michael addition, wherein the reaction is controlled by the TBDMS group and the (*E/Z*) isomers. The controlling TBDMS group may be removed again by the method of *T. Otten* ^[12] with *n*-BuNF₄ / NH₄F / HF as the elimination reagent, the publication of *T. Otten* ^[12] being part of the disclosure. This is another possibility for synthesising all four stereoisomers mutually independently.

PCT/EP01/10626

WO 02/22569

Since the initially presented, alternative synthesis still also offers the possibility of asymmetric catalysis on protonation of the silyl enol ether 45, this route is the better alternative. The second alternative route may possibly also suffer the problem of silyl group elimination, as the N-formyl group may sometimes also be eliminated under the elimination conditions to form the hydrofluoride.

10 **Example 8:**

Experimental conditions:

Comments on preparative operations

A) Protective gas method

15

All air- and moisture-sensitive reactions were performed under an argon atmosphere in evacuated, heat treated flasks sealed with septa.

20 Liquid components or components dissolved in solvent were added using plastic syringes fitted with V2A hollow needles. Solids were introduced through a countercurrent stream of argon.

25 **B) Solvents**

Solvent absorption was carried out on predried and prepurified solvents:

30 <i>Tetrahydrofuran:</i>	Four hours' refluxing over calcium hydride followed by distillation.
<i>Abs. tetrahydrofuran:</i>	Two hours' refluxing of pretreated THF over sodium-lead alloy under argon followed by distillation.

PCT/EP01/10626

WO 02/22569

- Dichloromethane:* Four hours' refluxing over calcium hydride followed by distillation through a 1 m packed column.
- 5 *Abs. dichloromethane:* Shaking of the pretreated dichloromethane with conc. sulfuric acid, neutralisation, drying, two hours' refluxing over calcium hydride under argon followed by distillation.
- 10 *Pentane:* Two hours' refluxing over calcium hydride followed by distillation through a 1 m packed column.
- Diethyl ether:* Two hours' refluxing over KOH followed by distillation through a 1 m packed column.
- 15 *Abs. diethyl ether:* Two hours' refluxing over sodium-lead alloy under argon followed by distillation.
- Toluene:* Two hours' refluxing over sodium wire followed by distillation through a 0.5 m packed column.
- 20 *Abs. toluene:* Two hours' refluxing over sodium-lead alloy followed by distillation.
- 25 *Methanol:* Two hours' refluxing over magnesium/magnesium methanolate followed by distillation.

C) Reagents used

30

- Argon:* Argon was purchased from Linde.
- n-Butyllithium:* n-BuLi was obtained as a 1.6 molar solution in hexane from Merck.
- (S,S)-(-)-1,2-diphenyl-*

PCT/EP01/10626

WO 02/22569

1,2-ethanediol: was purchased from Aldrich.
Benzyl mercaptan: was purchased from Aldrich
Ethyl mercaptan: was purchased from Fluka.
2-Heptanone: was purchased from Fluka.

5

All remaining reagents were purchased from the companies Aldrich, Fluka, Merck and Acros or were available to the working group.

10 D) Reaction monitoring

Thin-layer chromatography was used for reaction monitoring and for detection after column chromatography (see section 3.1.5). TLC was performed on silica gel coated glass sheets
15 with a fluorescence indicator (Merck, silica gel 60, 0.25 mm layer). Detection was achieved by fluorescence quenching (absorption of UV light of a wavelength of 254 nm) and by dipping in Mostain reagent [5% solution of $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}$ in 10% sulfuric acid (v/v) with addition of 0.3%
20 $\text{Ce}(\text{SO}_4)_2$] followed by heating in a stream of hot air.

E) Product purification

The substances were mainly purified by column
25 chromatography in glass columns with an integral glass frit and silica gel 60 (Merck, grain size 0.040-0.063 mm). An overpressure of 0.1-0.3 bar was applied. The eluents were generally selected such that the R_f value of the substance to be isolated was 0.35. The composition of the solvent
30 mixtures was measured volumetrically. The diameter and length of the column was tailored to the separation problem and the quantity of substance.

PCT/EP01/10626

WO 02/22569

Some crystalline substances were also purified by recrystallisation in suitable solvents or mixtures.

F) Analysis

- | | | |
|----|---|---|
| 5 | <i>HPLC_{preparative}</i> | Gilson Abimed; column: Hibar® ready-to-use column (25 cm x 25 mm) from Merck and UV detector. |
| | <i>HPLC_{analytical}</i> : | Hewlett Packard, column: Daicel OD, UV detector |
| 10 | <i>¹H-NMR spectroscopy:</i> | Varian GEMINI 300 (300 MHz) and Varian Inova 400 (400 MHz) with tetramethylsilane as internal standard. |
| 15 | <i>¹³C-NMR spectroscopy:</i> | Varian GEMINI 300 (75 MHz) and Inova 400 (100 MHz) with tetramethylsilane as internal standard. |
| | <i>2D-NMR spectroscopy:</i> | Varian Inova 400. |
| 20 | <i>Gas chromatography:</i> | Siemens Sichromat 2 and 3; FID detector, columns: OV-17-CB (fused silica, 25 m x 0.25 mm ID); CP-Sil-8 (fused silica, 30 m x 0.25 mm ID). |
| 25 | <i>IR spectroscopy:</i> | a) Measurements of KBr pellets: Perkin-Elmer FT/IR 1750.
b) Measurements in solution: Perkin-Elmer FT/IR 1720 X. |
| | <i>Mass spectroscopy:</i> | Varian MAT 212 (EL 70 eV, CL 100 eV). |
| 30 | <i>Elemental analysis:</i> | Heraeus CHN-O-Rapid, Elementar Vario EL. |
| | <i>Melting points:</i> | Tottoli melting point apparatus, Büchi 535. |

PCT/EP01/10626

WO 02/22569

G) Comments on analytical data

- Yields:* The stated yields relate to the isolated, purified products
- Boiling point/pressure:* The stated boiling temperatures were measured inside the apparatus with mercury thermometers and are uncorrected. The associated pressures were measured with analogous sensors.
- 10 *¹H-NMR spectroscopy:* The chemical shifts δ are stated in ppm against tetramethylsilane as internal standard, and the coupling constants J are stated in hertz (Hz). The following
- 15 abbreviations are used to describe signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet. cz denotes a complex zone of a spectrum. A prefixed br indicates a broad signal.
- 20 *¹³C-NMR spectroscopy:* The chemical shifts δ are stated in ppm with tetramethylsilane as internal standard.
- 25 *de values:* Diastereomeric excesses (de) are determined with the assistance of the ¹³C-NMR-spectra of the compounds. This method exploits the different shifts of
- 30 diastereomeric compounds in the proton-decoupled ¹³C spectrum.
- IR spectroscopy:* The position of the absorption bands ($\tilde{\nu}$) is stated in cm⁻¹. The following abbreviations are used

PCT/EP01/10626

WO 02/22569

to characterise the bands: vs = very strong, s = strong, m = moderate, w = weak, vw = very weak, br = broad.

5 *Gas chromatography:*

The retention time of the undecomposed compounds is stated in minutes. Details of measurement conditions are then listed: column used, starting temperature, temperature gradient, final temperature (in each case in °C) and the injection temperature T_s , if different from the standard temperature. (Sil 8: $T_s = 270^\circ\text{C}$, OV-17: $T_s = 280^\circ\text{C}$)

10

15

Mass spectroscopy:

The masses of the fragment ions (m/z) are stated as a dimensionless number, the intensity of which is a percentage of the base peak (rel. intensity). High intensity signals ($> 5\%$) or characteristic signals are stated.

20

Elemental analysis:

Values are stated as mass percentages [%] of the stated elements. The samples were deemed authentic at $\Delta_{C,H,N} \leq 0.5\%$.

25

Example 10:

General procedures (GP)

30 **Preparation of glycine alkyl ester hydrochlorides [GP 1]**

1.2 equivalents of thionyl chloride are introduced into 0.6 ml of alcohol per mmol of glycine with ice cooling to -10°C . After removal of the ice bath, 1 equivalent of

PCT/EP01/10626

WO 02/22569

glycine is added in portions. The mixture is stirred for 2 hours while being refluxed. After cooling to room temperature, the excess alcohol and the thionyl chloride are removed in a rotary evaporator. The resultant white solid is combined twice with the alcohol and the latter is again removed in the rotary evaporator in order to remove any adhering thionyl chloride completely.

10 **Preparation of formylaminoacetic acid alkyl esters [GP 2]**

1 equivalent of glycine alkyl ester hydrochloride is suspended in 0.8 ml of ethyl or methyl formate per mmol of glycine alkyl ester hydrochloride. 130 mg of toluenesulfonic acid are added per mol of glycine alkyl ester hydrochloride and the mixture is refluxed. 1.1 equivalents of triethylamine are now added dropwise to the boiling solution and the reaction solution is stirred overnight while being refluxed. After cooling to RT, the precipitated ammonium chloride salt is filtered out, the filtrate is evaporated to approx. 20% of its original volume and cooled to -5°C. The reprecipitated ammonium chloride salt is filtered out, the filtrate evaporated and distilled at 1 mbar.

25 **Preparation of isocyanoacetic acid alkyl ester [GP 3]**

1 equivalent of formylaminoacetic acid alkyl ester and 2.7 equivalents of diisopropylamine are introduced into DCM (10 ml per mmol formylaminoacetic acid alkyl ester) and cooled to -3°C with an ice bath. 1.2 equivalents of phosphoryl chloride are then added dropwise and the mixture is then stirred for a further hour at this temperature. Once the ice bath has been removed and room temperature reached, the mixture is cautiously hydrolysed with 1 ml of

PCT/EP01/10626

WO 02/22569

20% sodium carbonate solution per mmol of formylaminoacetic acid alkyl ester. After approx. 20 min, vigorous foaming is observed and the flask has to be cooled with ice water. After 60 minutes' stirring at RT, further water (1 ml per 5 mmol of formylaminoacetic acid alkyl ester) and DCM (0.5 ml per mmol formylaminoacetic acid alkyl ester) are added. The phases are separated and the organic phase is washed twice with 5% Na₂CO₃ solution and dried over MgSO₄. The solvent is removed in a rotary evaporator and the remaining brown oil 10 is distilled.

Preparation of (E)- and (Z)-2-formylamino-3-dialkyl-2-propenoic acid alkyl esters [GP4]

15 1.05 equivalents of potassium tert.-butanol in 0.7 ml of THF per mmol of isocyanoacetic acid alkyl ester are cooled to -78°C. To this end, a solution prepared from 1.0 equivalent of isocyanoacetic acid alkyl ester in 0.25 ml of THF per mmol is slowly added and the mixture is stirred at 20 this temperature for 30 min (→ pink-coloured suspension). A solution of 1.0 equivalent of ketone in 0.125 ml of THF per mmol is now added dropwise. After 30 minutes' stirring at -78°C, the temperature is raised to RT (1 h) and 1.05 equivalents of glacial acetic acid are added in a single 25 portion (yellow solution) and the mixture is stirred for a further 20 minutes. The solvent is removed in a rotary evaporator (40°C bath temperature). The crude product is obtained as a solid. The solid is suspended in 1.5 ml of diethyl ether per mmol and 0.5 ml water is added per 30 equivalent. The clear phases are separated and the aqueous phase extracted twice with diethyl ether. The combined organic phases are washed with saturated NaHCO₃ solution and dried over MgSO₄. After removal of the solvent, a waxy solid

PCT/EP01/10626

WO 02/22569

is obtained. The (*E*) and (*Z*) products can be separated by chromatography with diethyl ether/pentane (4:1) as eluent.

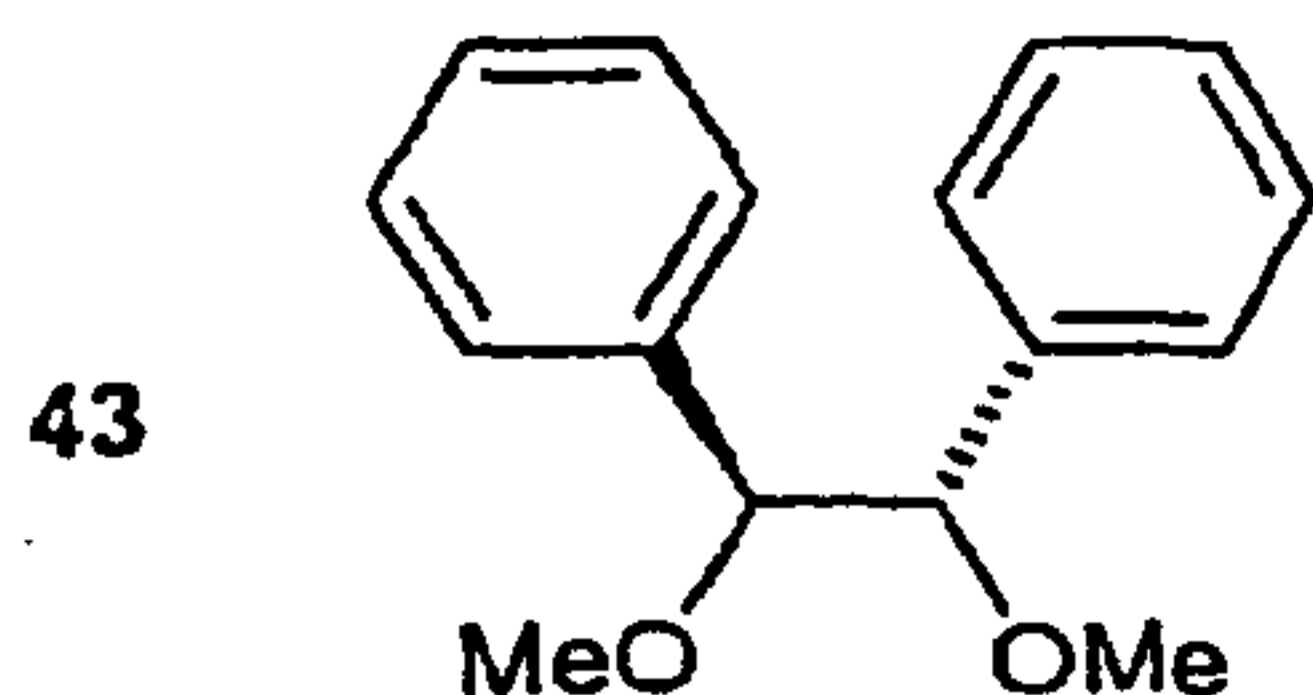
5 **Preparation of 2-formylamino-3-dialkyl-3-alkylsulfanylpropanoic acid alkyl ester [GP5]**

0.1 equivalents of butyllithium are introduced into 50 ml of THF per mmol and are cooled to 0°C. 10 equivalents of the mercaptan are now added dropwise. After 20 minutes' stirring, the solution is cooled to a temperature between -40 and 0°C and 1 equivalent of the 2-formylamino-3-dialkyl-2-propenoic acid alkyl ester in 5 ml of THF per mmol is slowly added. The mixture is stirred at the established temperature for 2 h and the temperature is then raised to 0°C and the mixture hydrolysed with 5% sodium hydroxide solution. The phases are separated and the aqueous phase is extracted twice with DCM. The combined organic phases are dried over MgSO₄ and the solvent is removed in a rotary evaporator. The mercaptan, which was introduced in excess, may be separated by means of chromatography with DCM/diethyl ether (6:1) as eluent.

Example 11:

25 **Special procedures and analytical data**

A) (*S,S*)-(-)-1,2-dimethoxy-1,2-diphenylethane ((*S,S*)-43)



M = 242.32 g/mol

30

PCT/EP01/10626

WO 02/22569

140 mg of NaH (60% in paraffin) are washed three times with pentane and dried under a high vacuum. The resultant material is then suspended in 5 ml of abs. THF. 250 mg (1.17 mmol) of (*S,S*)-(-)-2,2-diphenyl-2,2-ethanediol (**42**) dissolved in 3 ml of THF are now added dropwise. After the addition, the mixture is stirred for 30 minutes while being refluxed and is then cooled to 5°C. 310 mg of dimethyl sulfate are slowly added dropwise and the mixture is stirred for a further 30 min with ice cooling. The ice bath is removed and the reaction mixture raised to RT, wherein a viscous white solid is obtained which is stirred overnight at RT. The reaction is terminated by the addition of 5 ml of saturated NH₄Cl solution. The phases are separated and the aqueous phase is extracted twice with diethyl ether. The combined organic phases are washed first with saturated NaHCO₃ solution and then with brine and dried over MgSO₄. After removal of the solvent in a rotary evaporator, a colourless solid is obtained which is recrystallised in pentane (at -22°C). The dimethyl ether is now obtained in the form of colourless needles.

Yield: 204 mg (0.84 mmol, 72% of theory)
mp: 98.5°C (Lit.: 99-100°C) ^[39]
GC: R_t = 3.08 min (OV-17, 160-10-260)

¹H-NMR spectrum (400 MHz, CDCl₃):

δ = 7.15 (m, 6 H, H_{Ar}), 7.00 (m, 4 H, H_{Ar}), 4.31 (s, 2 H, CH₂OCH₃), 3.27 (s, 6 H, CH₃) ppm.

¹³C-NMR spectrum (100 MHz, CDCl₃):

δ = 138.40 (C_{Ar}, quart.), 128.06 (4xHC_{Ar}), 127.06 (HC_{Ar}, para), 87.98 (CH₃), 57.47 (HCOCH₃) ppm.

IR spectrum (KBr pellet):

PCT/EP01/10626

WO 02/22569

$\tilde{\nu}$ = 3448 (br m), 3082 (vw), 3062 (m), 3030 (s), 2972 (s),
 2927 (vs), 2873 (s), 2822 (vs), 2583 (vw), 2370 (vw), 2179
 (vw), 2073 (vw), 1969 (br m), 1883 (m), 1815 (m), 1760 (w),
 1737 (vw), 1721 (vw), 1703 (w), 1686 (vw), 1675 (vw), 1656
 5 (w), 1638 (vw), 1603 (m), 1585 (w), 1561 (w), 1545 (w),
 1525 (vw), 1492 (s), 1452 (vs), 1349 (s), 1308 (m), 1275
 (w), 1257 (vw), 1215 (vs), 1181 (m), 1154 (m), 1114 (vs),
 1096 (vs), 1028 (m), 988 (s), 964 (s), 914 (m), 838 (s),
 768 (vs), 701 (vs), 642 (m), 628 (s), 594 (vs), 515 (s)
 10 [cm⁻¹].

Mass spectrum (Cl, isobutane):

M/z [%] = 212 (M⁺ + 1 - OMe, 16), 211, (M⁺ - MeOH, 100), 165
 (M⁺ - Ph, 2), 121 ($\frac{1}{2}$ M⁺, 15), 91 (Bn⁺, 3), 85 (M⁺ - 157, 8),
 15 81 (M⁺ - 161, 7), 79 (M⁺ - 163, 6), 71 (M⁺ - 171, 8).

Elemental analysis:

calc.: C = 79.31 H = 7.49

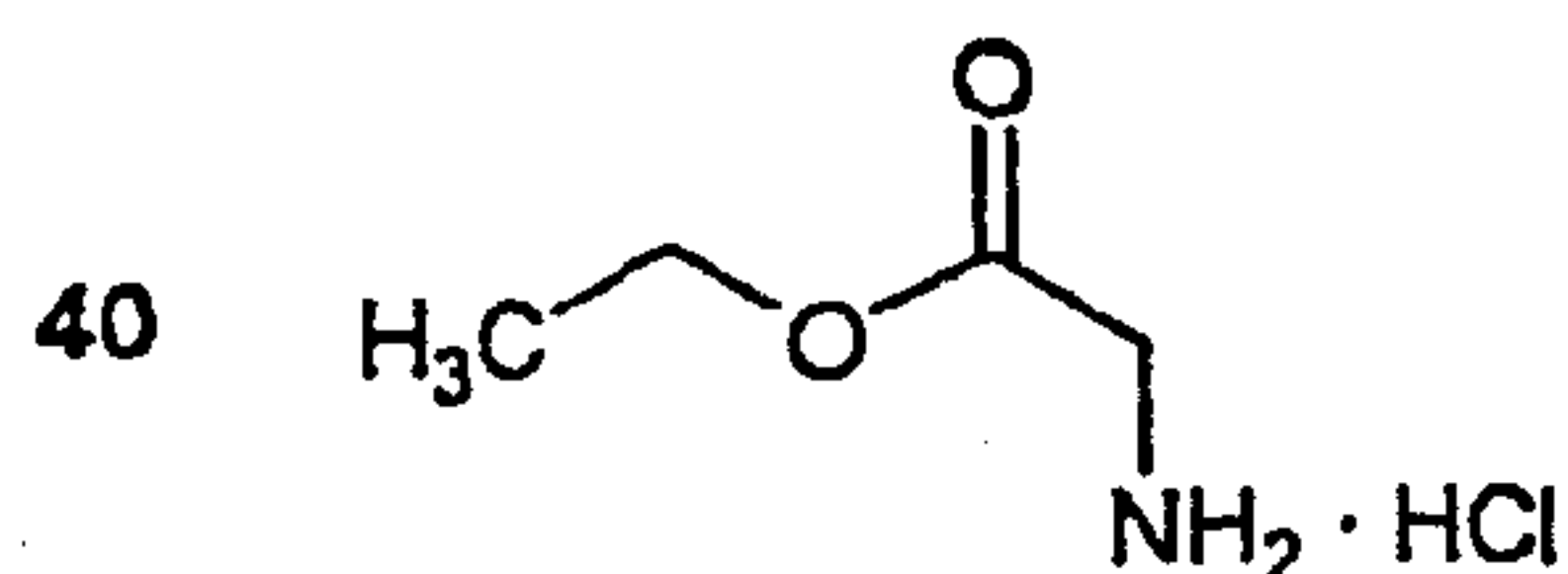
fd.: C = 79.12 H = 7.41

20

All other analytical data are in line with literature values ^[34].

B) Glycine ethyl ester hydrochloride (40)

25



M = 139.58 g/mol

In accordance with **GP 1**, 1000 ml of ethanol are reacted
 30 with 130 g (1.732 mol) of glycine **39** and 247.3 g (2.08 mol)
 of thionyl chloride. After recrystallisation from ethanol,

PCT/EP01/10626

WO 02/22569

a colourless, acicular solid is obtained, which is dried under a high vacuum.

Yield: 218.6g (1.565 mol, 90.4% of theory)

5 **GC:** $R_t = 1.93$ min (OV-17, 60-10-260)

mp.: 145°C (Lit.: 144°C)^[48]

¹H-NMR spectrum (300 MHz, CD₃OD):

$\delta = 4.30$ (q, $J = 7.14$, 2 H, OCH₂), 3.83 (s, 2 H, H₂CNH₂),
10 1.32 (tr, $J = 7.14$, 3 H, CH₃) ppm.

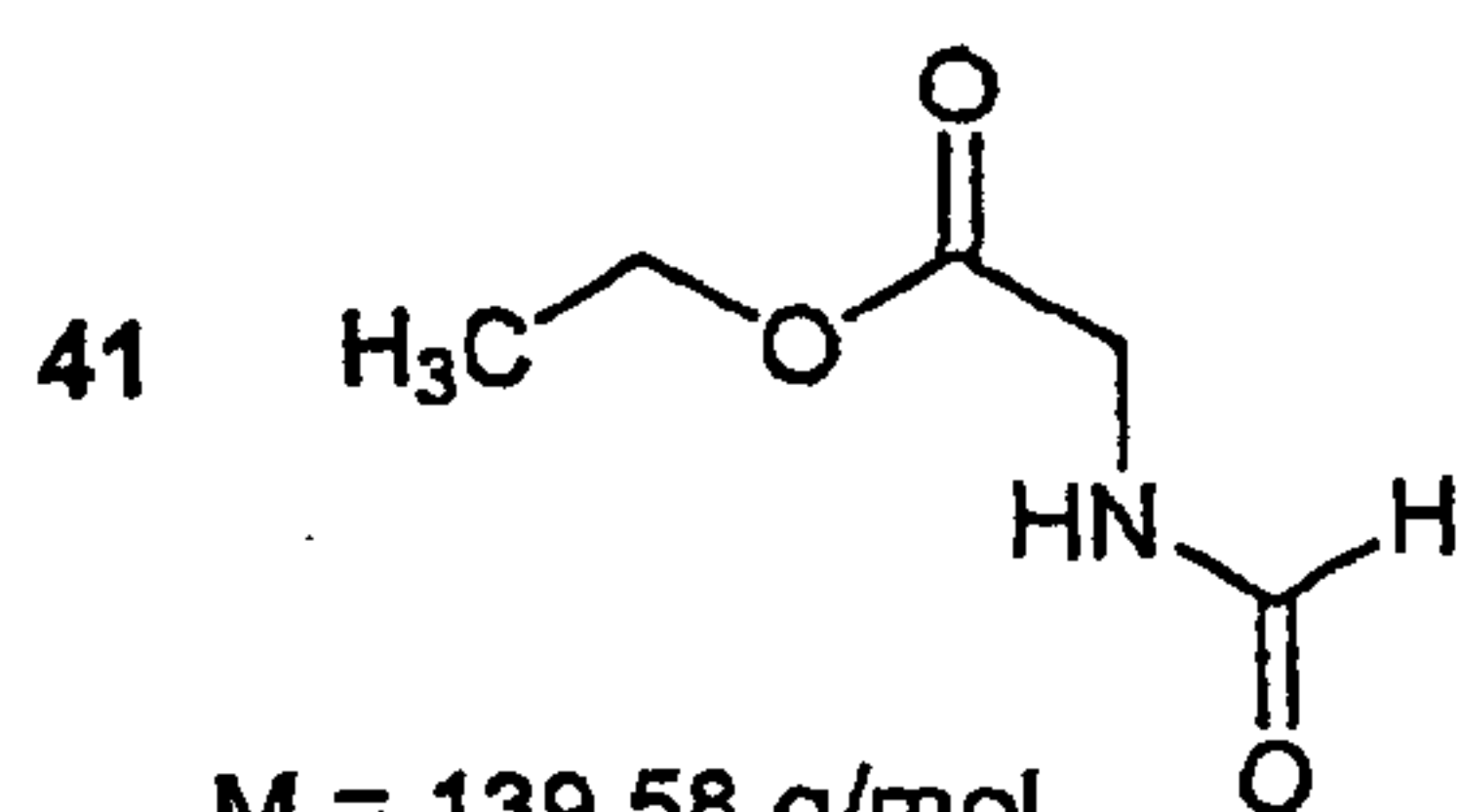
¹³C-NMR spectrum (75 MHz, CD₃OD):

$\delta = 167.53$ (C=O), 63.46 (OCH₂), 41.09 (H₂CNH₂), 14.39 (CH₃)
ppm.

15

All other analytical data are in line with literature values^[48].

C) N-formyl glycine ethyl ester (41)



20

In accordance with **GP 2**, 218 g (1.553 mol) of glycine ethyl ester hydrochloride **40**, 223 mg of toluenesulfonic acid and 178 g of triethylamine are reacted in 1.34 l of ethyl
25 formate. After distillation at 1 mbar, a colourless liquid is obtained.

Yield: 184.0 g (1.403 mol, 90.3% of theory)

GC: $R_t = 6.95$ min (CP-Sil 8, 60-10-300)

30 **bp.:** 117°C/1 mbar (Lit.: 119 - 120°C/1 mbar)^[49]

PCT/EP01/10626

WO 02/22569

A rotameric ratio of 94:6 around the N-CHO bond is obtained.

5 **¹H-NMR spectrum** (400 MHz, CDCl₃):

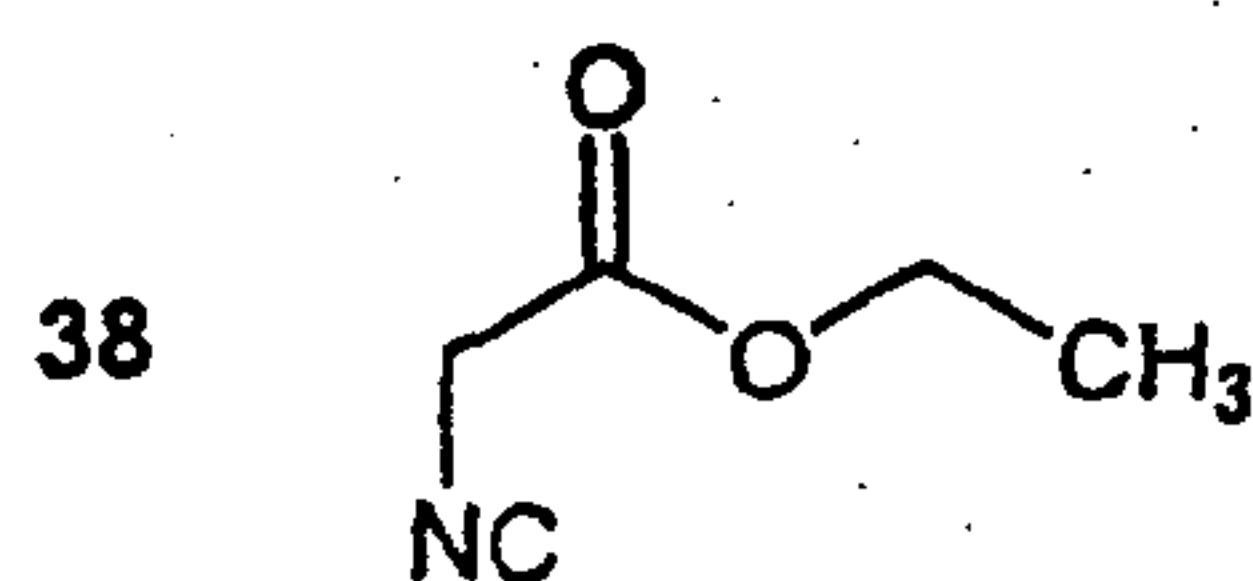
δ = 8.25, 8.04 (s, d, J = 11.81, 0.94 H, 0.06 H, HC=O), 4.22 (dq, J = 7.14, 3.05, 2 H, OCH₂), 4.07 (d, J = 5.50, 2 H, H₂CC=O), 1.29 (tr, J = 7.14, 3 H, CH₃) ppm.

10 **¹³C-NMR spectrum** (100 MHz, CDCl₃):

δ = 169.40 (OC=O), 161.43 (HC=O), 61.55 (OCH₂), 39.90 (H2CNH₂), 14.10 (CH₃) ppm.

All other analytical data are in line with literature values ^[49].

D) Isocyanoacetic acid ethyl ester (38)



M = 113.12 g/mol

20

In accordance with **GP 3**, 50 g (381 mmol) of formyl glycine ethyl ester **41**, 104 g (1.028 mol) of diisopropylamine and 70.1 g (457 mmol) of phosphoryl chloride are reacted in 400 ml of DCM. After distillation at 5 mbar a slightly yellow liquid is obtained.

25

Yield: 34.16g (302 mmol, 79.3% of theory)
GC: R_t = 1.93 min (OV-17, 50-10-260)
bp.: 77°C/5 mbar (Lit.: 89-91°C/20 mbar) ^[50]

30

¹H-NMR spectrum (300 MHz, CDCl₃):

PCT/EP01/10626

WO 02/22569

δ = 4.29 (q, J = 7.14, 2 H, OCH_2), 4.24 (d, J = 5.50, 2 H, $\text{H}_2\text{CC}=\text{O}$), 1.33 (tr, J = 7.14, 3 H, CH_3) ppm.

^{13}C -NMR spectrum (75 MHz, CDCl_3):

5 δ = 163.75 ($\text{OC}=\text{O}$), 160.87 (NC), 62.72 (OCH_2), 43.58 (H_2CNH_2), 14.04 (CH_3) ppm.

IR-spectrum (capillary):

10 $\tilde{\nu}$ = 2986 (s), 2943 (w), 2426 (br vw), 2164 (vs, NC), 1759 (vs, C=O), 1469 (w), 1447 (w), 1424 (m), 1396 (vw), 1375 (s), 1350 (s), 1277 (br m), 1213 (vs), 1098 (m), 1032 (vs), 994 (m), 937 (vw), 855 (m), 789 (br m), 722 (vw), 580 (m), 559 (w) [cm^{-1}].

15 Mass spectrum (Cl, isobutane):

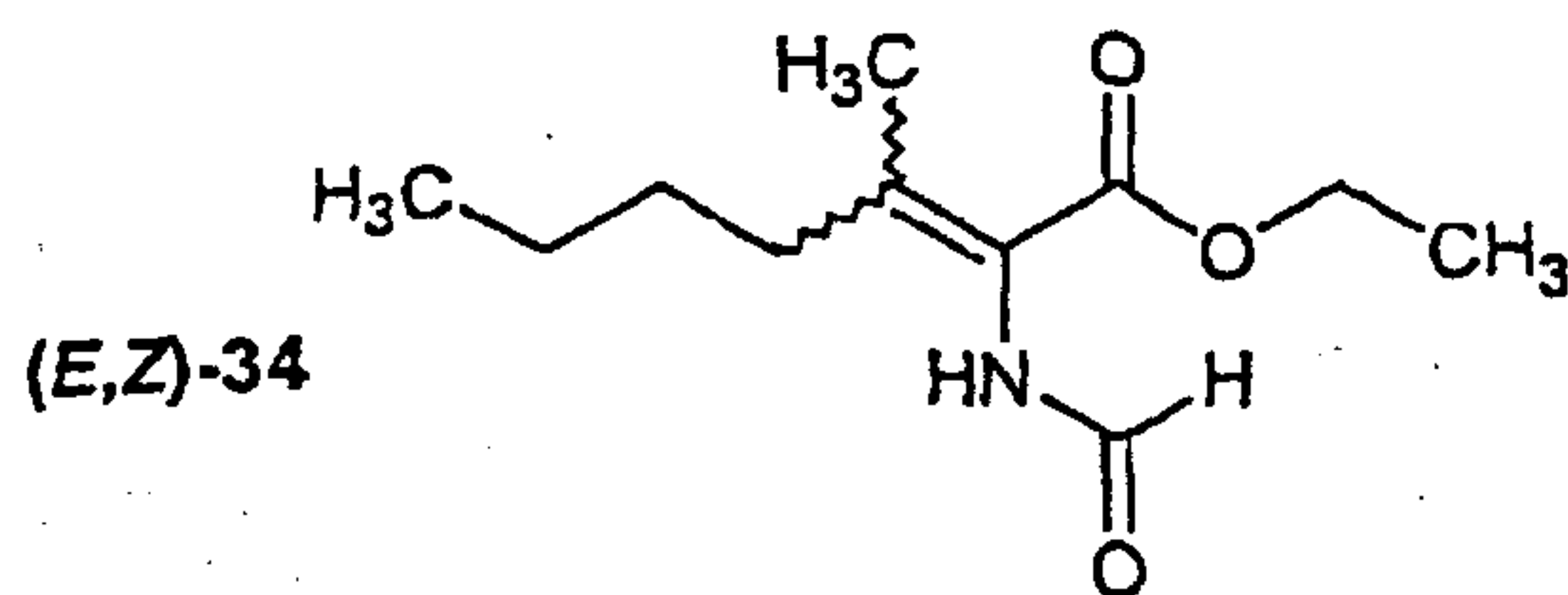
M/z [%] = 171 (M^+ + isobutane, 6), 170 (M^+ + isobutane -1, 58), 114 (M^+ + 1, 100), 113 (M^+ , 1), 100 (M^+ - 13, 2), 98 (M^+ - CH_3 , 2), 87 (M^+ - C_2H_5 +1, 1), 86 (M^+ - C_2H_5 , 18), 84 (M^+ - 29, 2).

20

All other analytical data are in line with literature values ^[50].

E) (E)- and (Z)-2-formylamino-3-methyl-2-octenoic acid

25 ethyl ester ((E,Z)-34)



M = 227.31 g/mol

According to GP 4, 15 g (132 mmol) of isocyanoacetic acid
30 ethyl ester 38, 15.6 g (139 mmol) of potassium tert.-

PCT/EP01/10626

WO 02/22569

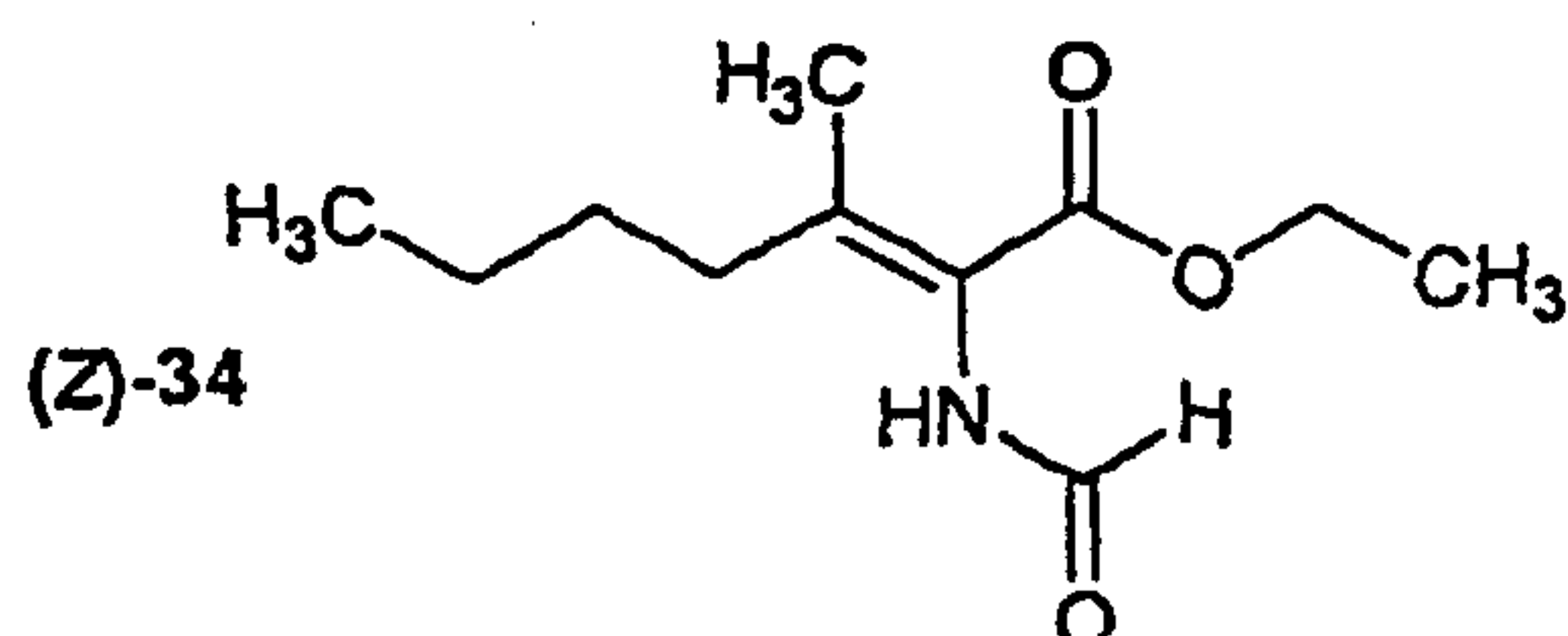
butanolate, 15.1 g (132 mmol) of 2-heptanone **37** and 8.35 g (139 mmol) of glacial acetic acid are reacted.

The (E) and (Z) products are separated from one another by chromatography with diethyl ether/pentane (4:1) as eluent:

5

Yield:	11.52 g	(50.7 mmol, 38.0% of theory)
		(Z) product
	9.07 g	(39.9 mmol, 30.2% of theory)
		(E) product
10	1.32 g	(5.8 mmol, 4.4% of theory)
		mixed fraction

F) (Z)-2-formylamino-3-methyl-2-octenoic acid ethyl ester
((Z)-34)



15

GC:	$R_t = 12.96$ min	(CP-Sil 8, 80-10-300)
mp.:	57°C	(colourless, amorphous)
TLC:	$R_f = 0.32$	(ether:pentane - 4:1)
	$R_f = 0.34$	(DCM:ether - 4:1)

20

A rotameric ratio of 65:35 around the N-CHO bond is obtained.

¹H-NMR spectrum (400 MHz, CDCl₃):

25 $\delta = 8.21, 7.95$ (d, d, $J = 1.38, 11.40, 0.65, 0.35$ H, HC=O),
 6.80, 6.69 (br s, br d, $J = 11.40, 0.65, 0.35$ H, HN), 4.22
 (dq, $J = 1.10, 7.14, 2$ H, OCH₂), 2.23 (dtr, $J = 7.97,$
 38.73, 2 H, C=CCH₂), 2.20 (dd, $J = 1.10, 21.7, 3$ H, C=CCH₃),
 1.45 (dquin, $J = 1.25, 7.97, 2$ H, CCH₂CH₂), 1.30 (dquin, $J =$
 30 4.12, 7.14, 4 H, CH₃CH₂CH₂), 1.30 (m, 3 H, OCH₂CH₃), 0.89
 (tr, $J = 7.00, 3$ H, CH₂CH₃) ppm.

PCT/EP01/10626

WO 02/22569

¹³C-NMR spectrum (100 MHz, CDCl₃):

δ = 164.82, 164.36 (OC=O), 159.75 (HC=O), 152.72, 150.24
 (C=CNH), 120.35, 119.49 (C=CCH₃), 61.11, 60.89 (OCH₂),
 5 35.82, 35.78 (CH₂), 31.80, 31.72 (CH₂), 27.21, 26.67 (CH₂),
 22.45, 22.42 (CH₂), 19.53, 19.17 (C=CCH₃), 14.18 (OCH₂CH₃),
 13.94, 13.90 (CH₂CH₃) ppm.

IR spectrum (KBr pellet):

10 $\tilde{\nu}$ = 3256 (vs), 2990 (w), 2953 (w), 2923 (m), 2872 (w), 2852
 (w), 2181 (br vw), 1711 (vs, C=O), 1659 (vs, OC=O), 1516
 (s), 1465 (s), 1381 (s), 1310 (vs), 1296 (vw), 1269 (m),
 1241 (s), 1221 (s), 1135 (w), 1115 (vw), 1032 (vs), 1095
 (s), 1039 (m), 884 (m), 804 (m), 727 (vw), 706 (vw), 590
 15 (w), 568 (vw) [cm⁻¹].

Mass spectrum (EI, 70 eV):

M/z [%] = 227 (M⁺, 19), 182 (M⁺ - EtOH+1, 24), 181 (M⁺ -
 EtOH, 100) 170 (M⁺ - 57, 9), 166 (M⁺ - 61, 8), 156 (M⁺ - 71,
 20 5), 154 (M⁺ - HCO₂Et+1, 6), 153 (M⁺ - HCO₂Et, 13), 152 (M⁺ -
 HCO₂Et-1, 13), 142 (M⁺ - 85, 15), 139 (M⁺ - HCO₂Et- CH₃ + 1,
 8), 138 (M⁺ - HCO₂Et - CH₃, 65), 126 (M⁺ - HCO₂Et- CHO + 2,
 16), 125 (M⁺ - HCO₂Et- CHO + 1, 34), 124 (M⁺ - HCO₂Et- CHO,
 51), 114 (M⁺ - 113, 36), 111 (M⁺ - HCO₂Et-HNCHO + 1, 17),
 25 110 (M⁺ - HCO₂Et - HNCHO, 36), 109 (M⁺ - HCO₂Et- HNCHO -1,
 20), 108 (M⁺ - HCO₂Et- HNCHO - 2, 10), 98 (M⁺ - 129, 6), 97
 (M⁺ - 130, 9), 96 (M⁺ - 131, 12), 82 (M⁺ - 145, 10), 68 (M⁺ -
 159, 48), 55 (M⁺ - 172, 12).

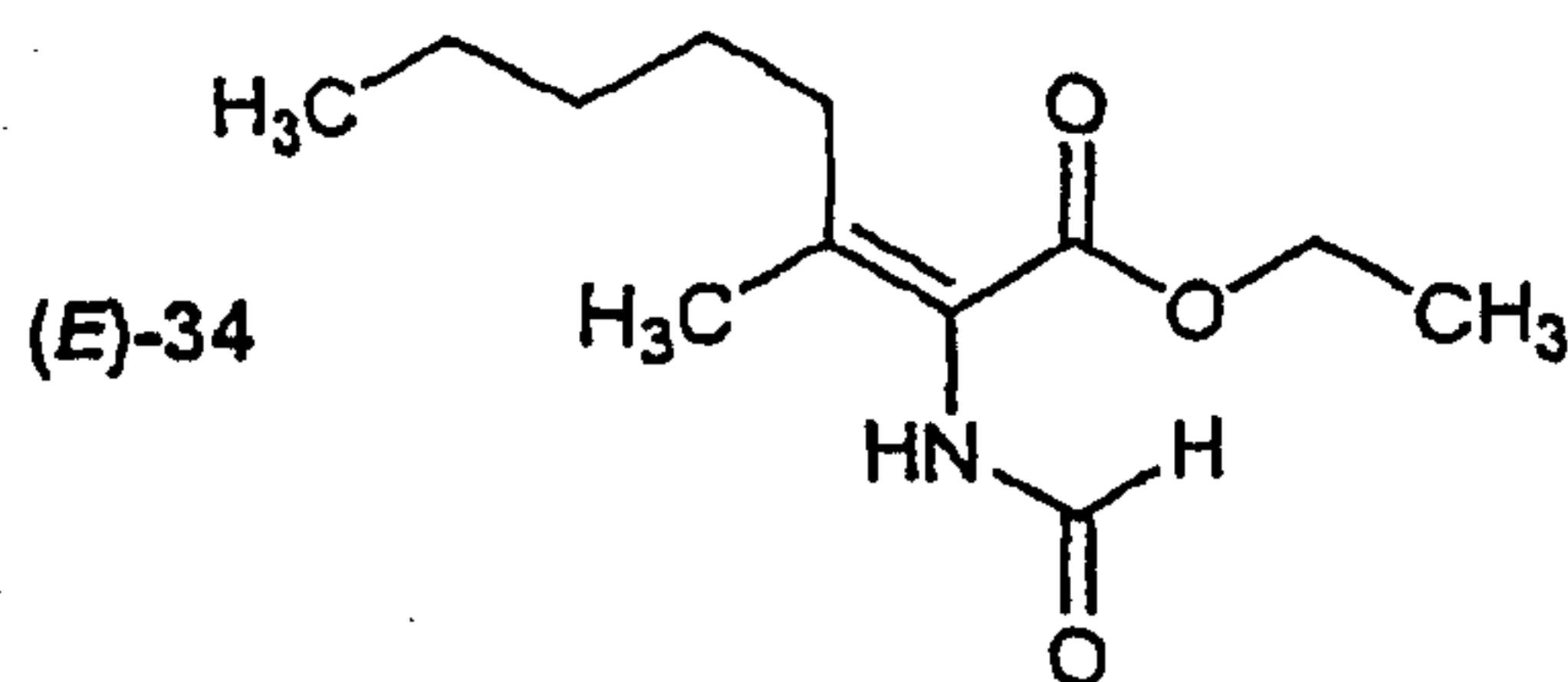
30 **Elemental analysis:**

calc.: C = 63.41 H = 9.31 N = 6.16
 fd.: C = 63.51 H = 9.02 N = 6.15

PCT/EP01/10626

WO 02/22569

**G) (E)-2-formylamino-3-methyl-2-octenoic acid ethyl ester
(E)-34**



GC:	$R_t = 13.71$ min	(CP-Sil 8, 80-10-300)
5 mp.:	53°C	(colourless, amorphous)
TLC:	$R_f = 0.20$	(ether:pentane - 4:1)
	$R_f = 0.26$	(DCM:ether - 4:1)

A rotameric ratio of 65:35 around the N-CHO bond is
10 obtained.

$^1\text{H-NMR}$ spectrum (400 MHz, CDCl_3):

$\delta = 8.16, 7.96$ (dd, $J = 1.64, 11.68, 0.65, 0.35$ H, HC=O),
6.92, 6.83 (br s, br d, $J = 11.68, 0.65, 0.35$ H, HN), 4.23
15 (dq, $J = 0.82, 7.14, 2$ H, OCH_2), 2.56 (dtr, $J = 7.96, 18.13,$
2 H, C=CCH_2), 1.90 (dd, $J = 0.55, 39.55, 3$ H, C=CCH_3), 1.51
(m, 2 H, CCH_2CH_2), 1.32 (dquin, $J = 2.48, 7.14, 4$ H,
 $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.32 (m, 3 H, OCH_2CH_3), 0.90 (dtr, $J = 3.57,$
7.14, 3 H, CH_2CH_3) ppm.

20

$^{13}\text{C-NMR}$ spectrum (100 MHz, CDCl_3):

$\delta = 164.75, 164.14$ (OC=O), 158.96 (HC=O), 151.38, 150.12
(C=CNH), 120.74, 119.48 (C=CCH_3), 61.10, 60.90 (OCH_2), 35.59
(CH_2), 31.90 (CH_2), 28.09, 28.04 (CH_2), 22.48 (CH_2), 20.89
25 (C=CCH_3), 14.17 (OCH_2CH_3), 13.99 (CH_2CH_3) ppm.

IR spectrum (KBr pellet):

$\tilde{\nu} = 3276$ (vs), 2985 (w), 2962 (w), 2928 (m), 2859 (m), 2852
(w), 1717 (vs, C=O), 1681 (s, OC=O), 1658 (vs, OC=O), 1508
30 (s), 1461 (s), 1395 (s), 1368 (vw), 1301 (vs), 1270 (w),

PCT/EP01/10626

WO 02/22569

1238 (m), 1214 (s), 1185 (m), 1127 (m), 1095 (s), 1046 (m),
1027 (w), 932 (m), 886 (s), 793 (m), 725 (br s), 645 (m),
607 (m), 463 (w) [cm^{-1}].

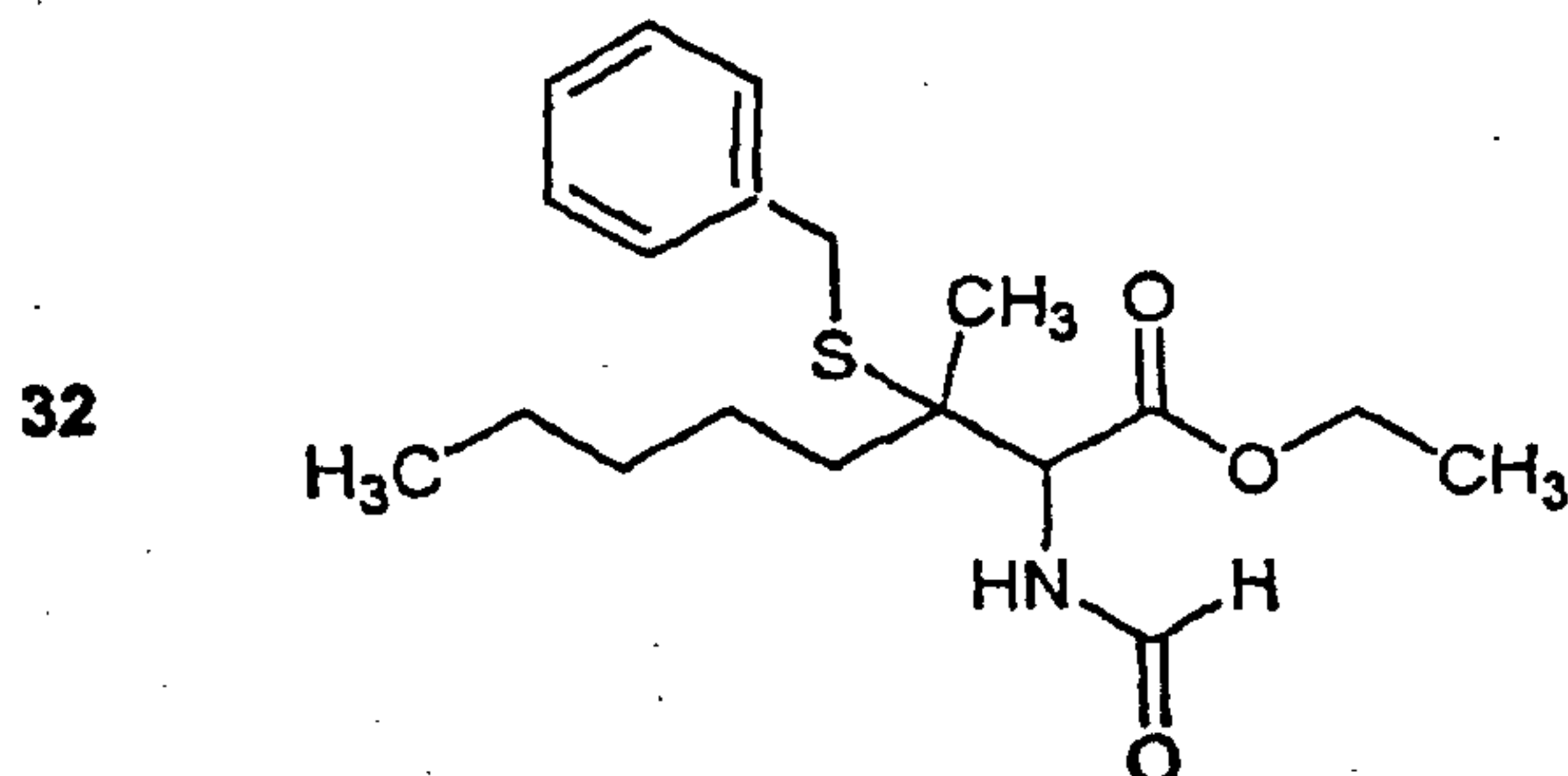
5 **Mass spectrum** (EI, 70 eV):

M/z [%] = 227 (M^+ , 19), 182 ($\text{M}^+ - \text{EtOH} + 1$, 20), 181 ($\text{M}^+ - \text{EtOH}$, 100), 170 ($\text{M}^+ - 57$, 8), 166 ($\text{M}^+ - 61$, 8), 156 ($\text{M}^+ - 71$, 7), 154 ($\text{M}^+ - \text{HCO}_2\text{Et} + 1$, 6), 153 ($\text{M}^+ - \text{HCO}_2\text{Et}$, 14), 152 ($\text{M}^+ - \text{HCO}_2\text{Et} - 1$, 12), 142 ($\text{M}^+ - 85$, 151), 139 ($\text{M}^+ - \text{HCO}_2\text{Et} - \text{CH}_3 + 1$, 8), 138 ($\text{M}^+ - \text{HCO}_2\text{Et} - \text{CH}_3$, 58), 126 ($\text{M}^+ - \text{HCO}_2\text{Et} - \text{CHO} + 2$, 13), 125 ($\text{M}^+ - \text{HCO}_2\text{Et} - \text{CHO} + 1$, 32), 124 ($\text{M}^+ - \text{HCO}_2\text{Et} - \text{CHO}$, 46), 114 ($\text{M}^+ - 113$, 31), 111 ($\text{M}^+ - \text{HCO}_2\text{Et} - \text{HNCHO} + 1$, 16), 110 ($\text{M}^+ - \text{HCO}_2\text{Et} - \text{HNCHO}$, 34), 109 ($\text{M}^+ - \text{HCO}_2\text{Et} - \text{HNCHO} - 1$, 18), 108 ($\text{M}^+ - \text{HCO}_2\text{Et} - \text{HNCHO} - 2$, 9), 98 ($\text{M}^+ - 129$, 5), 97 ($\text{M}^+ - 130$, 7), 96 ($\text{M}^+ - 131$, 11), 93 ($\text{M}^+ - 134$, 7), 82 ($\text{M}^+ - 145$, 9), 69 ($\text{M}^+ - 158$, 6), 68 ($\text{M}^+ - 159$, 43), 55 ($\text{M}^+ - 172$, 10).

Elemental analysis:

20 calc.: C = 63.41 H = 9.31 N = 6.16
fd.: C = 63.23 H = 9.38 N = 6.10

H) 3-Benzylsulfanyl-2-formylamino-3-methyloctanoic acid ethyl ester (32)



25

M = 351.51 g/mol

According to **GP 5**, 0.28 ml (0.44 mmol) of n-butyllithium, 5.5 g (44 mmol) of benzyl mercaptan **35** and 1 g (4.4 mmol) of 2-formylamino-3-methyl-2-octenoic acid ethyl ester (**34**)

PCT/EP01/10626

WO 02/22569

are reacted in 40 ml of abs. THF ($-78^{\circ}\text{C} \rightarrow \text{RT}$). The resultant colourless oil is purified by column chromatography with DCM/ether (6:1), wherein a colourless, high viscosity oil is obtained.

5

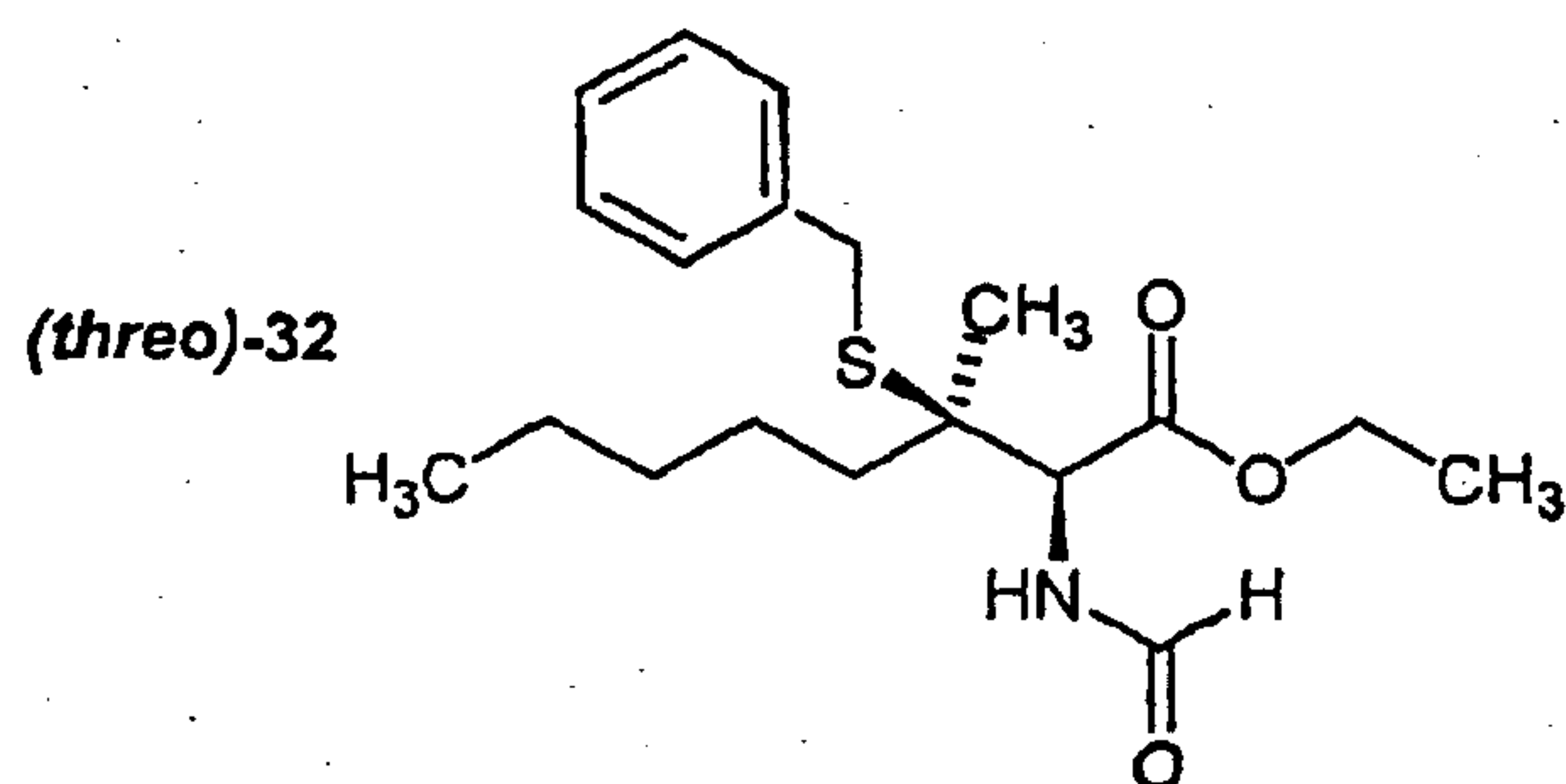
Yield: 1.51 g (43 mmol, 98% of theory)

TLC: $R_f = 0.51$ (DCM:ether - 6:1)

The resultant diastereomers may be separated from one another by preparative HPLC or by crystallisation in pentane/ethanol (10:1).

10

J) threo Diastereomer ((threo)-32):



15 **mp.:** 75°C (colourless, acicular, crystalline)

de: $> 96\%$ (according to ^{13}C -NMR)

HPLC_{prep.}: 19.38 min (ether:pentane - 85:15)

A rotameric ratio of 91:9 around the N-CHO bond is obtained.

20

^1H -NMR spectrum (400 MHz, CDCl_3):

$\delta = 8.22, 7.98$ (s, d, $J = 11.54, 0.91, 0.09$ H, HC=O), $7.21 - 7.32$ (cz, 5 H, CH_{ar}), $6.52, 6.38$ (dm, $J = 8.66, 0.91, 0.09$ H, HN), 4.74 (d, $J = 8.66, 1$ H, CHNH), 4.24 (ddq, $J = 17.85, 10.71, 7.14, 2$ H, OCH_2), 3.71 (s, 2 H, SCH_2), 1.56 (m, 3H, SCCH_3), 1.45 (dquin, $1.25, 7.97, 2$ H, CCH_2CH_2), $1.20 - 1.45$ (cz, 11 H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2+\text{OCH}_2\text{CH}_3$), 0.89 (dtr, $J = 3.3, 7.00, 3$ H, CH_2CH_3) ppm.

25

PCT/EP01/10626

WO 02/22569

 ^{13}C -NMR spectrum (100 MHz, CDCl_3):

δ = 170.37 ($\text{OC}=\text{O}$), 160.90 ($\text{HC}=\text{O}$), 137.31 (C_{Ar} , quart.), 129.31 (HC_{Ar}), 128.81 (HC_{Ar}), 127.41 (HC_{Ar} , para), 61.94 (OCH_2), 57.00 (CHNH), 52.30 (CS), 38.59 (CH_2), 33.31 (CH_2), 32.42 (CH_2), 24.00 (CH_2), 22.92 (CH_2), 22.51 (SCCH_3), 14.54 (OCH_2CH_3), 14.42 (CH_2CH_3) ppm.

IR spectrum (KBr pellet):

$\tilde{\nu}$ = 3448 (m), 3184 (br vs), 3031 (m), 2975 (m), 2929 (s), 2899 (w), 2862 (m), 1954 (w), 1734 (vs, $\text{C}=\text{O}$), 1684 (vs, $\text{OC}=\text{O}$), 1601 (w), 1561 (s), 1495 (m), 1468 (s), 1455 (m), 1296 (vw), 1441 (w), 1381 (vs), 1330 (s), 1294 (m), 1248 (s), 1195 (vs), 1158 (w), 1126 (s), 1096 (s), 1070 (w), 1043 (vw), 1028 (w), 1008 (s), 958 (m), 919 (w), 854 (s), 833 (m), 783 (s), 715 (vs), 626 (vw), 626 (m), 567 (vw) 483 (s) [cm^{-1}].

Mass spectrum (EI, 70 eV):

M/z [%] = 351 (M^+ , 1), 324 ($M^+ - \text{C}_2\text{H}_5$, 1), 306 ($M^+ - \text{C}_2\text{H}_5\text{OH} - 1$, 1), 278 ($M^+ - 73$, 1), 250 ($M^+ - \text{HCO}_2\text{Et} - \text{HCO}$, 1), 223 ($M^+ - 128$, 5), 222 ($M^+ - 129$, 16), 221 ($M^+ - \text{EtO}_2\text{CCHNHCHO}$, 100), 184 ($M^+ - 167$, 6), 91 ($M^+ - 260$, 71).

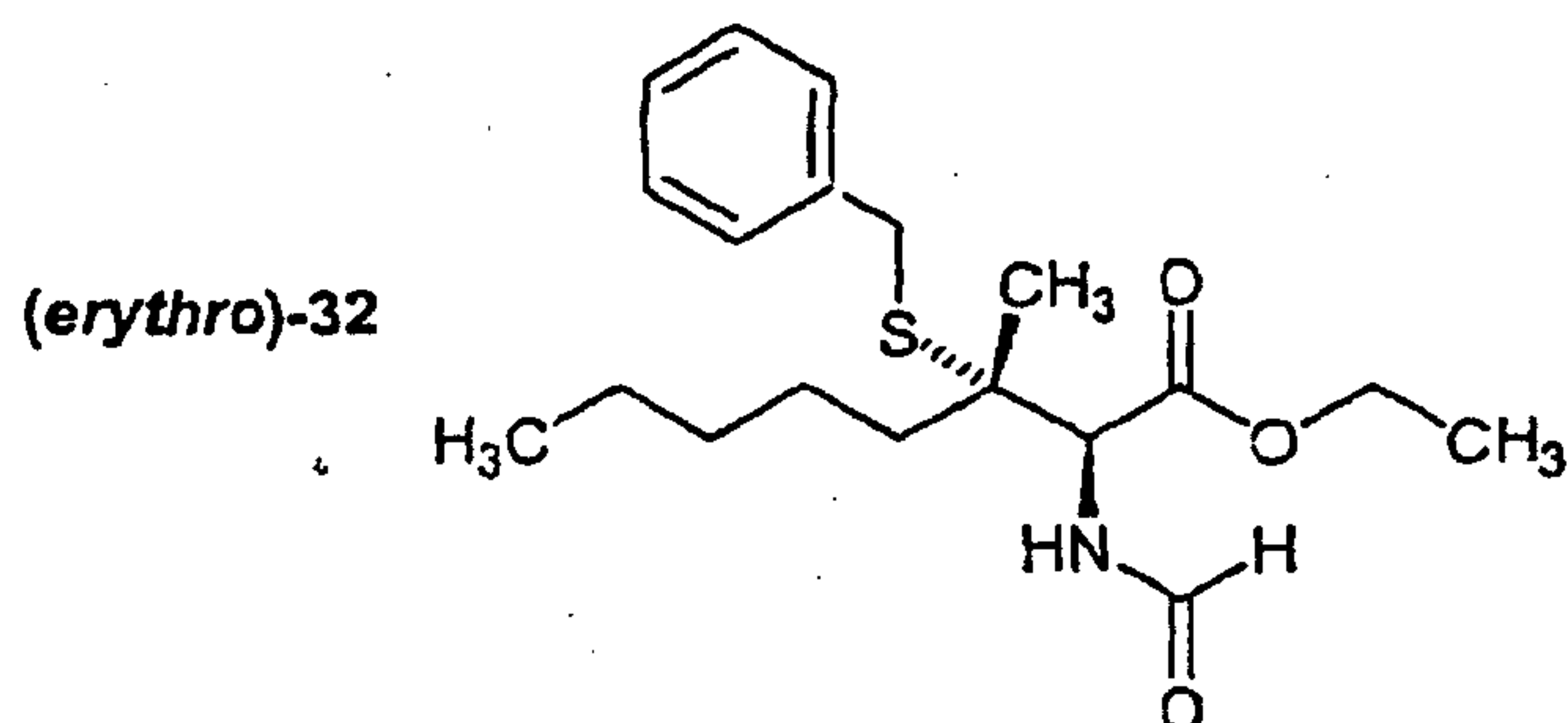
25 **Elemental analysis:**

calc.: C = 64.92 H = 8.32 N = 3.98

fd.: C = 64.88 H = 8.40 N = 3.92

PCT/EP01/10626

WO 02/22569

K) erythro Diastereomer ((erythro)-32):

Clear, oily liquid

de: 82% (according to ^{13}C -NMR)5 **HPLC_{prep.}:** 20.61 min (ether:pentane - 85:15)

A rotameric ratio of 91:9 around the N-CHO bond is obtained.

10 **^1H -NMR spectrum** (400 MHz, CDCl_3):

δ = 8.22, 7.97 (s, d, J = 11.54, 0.91, 0.09 H, HC=O), 7.20 - 7.34 (cz, 5 H, CH_{ar}), 6.61, 6.43 (br dm, J = 9.34, 0.91, 0.09 H, HN), 4.74 (d, J = 9.34, 1 H, CHNH), 4.24 (ddq, J = 17.85, 10.71, 7.14, 2 H, OCH_2), 3.77 (d, J = 11.53, 1 H, SCHH), 3.69 (d, J = 11.53, 1 H, SCHH), 1.70 (m, 2 H, CH_2), 1.52 (m, 2 H, CH_2), 1.17-1.40 (cz, 10 H, $\text{CH}_3\text{C} + 2 \times \text{CH}_2 + \text{OCH}_2\text{CH}_3$), 0.90 (tr, J = 7.14, 3 H, CH_2CH_3) ppm.

 ^{13}C -NMR spectrum (100 MHz, CDCl_3):

20 δ = 169.87 (OC=O), 160.49 (HC=O), 137.05 (C_{Ar} , quart.), 128.91 (HC_{Ar}), 128.40 (HC_{Ar}), 126.99 (HC_{Ar} , para), 61.52 (OCH_2), 56.81 (CHNH), 51.91 (CS), 37.51 (CH_2), 32.83 (CH_2), 32.13 (CH_2), 23.65 (CH_2), 23.19 (CH_2), 22.55 (SCCH_3), 14.11 (OCH_2CH_3), 14.03 (CH_2CH_3) ppm.

25

IR-spectrum (capillary):

PCT/EP01/10626

WO 02/22569

$\tilde{\nu}$ = 3303 (br vs), 3085 (vw), 3062 (w), 3029 (m), 2956 (vw), 2935 (vw), 2870 (w), 2748 (w), 1949 (br w), 1880 (br w), 1739 (vs, C=O), 1681 (vs, OC=O), 1603 (m), 1585 (vw), 1496 (br vs), 1455 (vs), 1381 (br vs), 1333 (s), 1197 (br vs),
 5 1128 (w), 1095 (m), 1070 (s), 1030 (vs), 971 (br w), 918 (m), 859 (s), 805 (vw), 778 (m), 714 (vs), 699 (vw), 621 (w), 569 (w) 484 (s) [cm^{-1}].

Mass spectrum (EI, 70 eV):

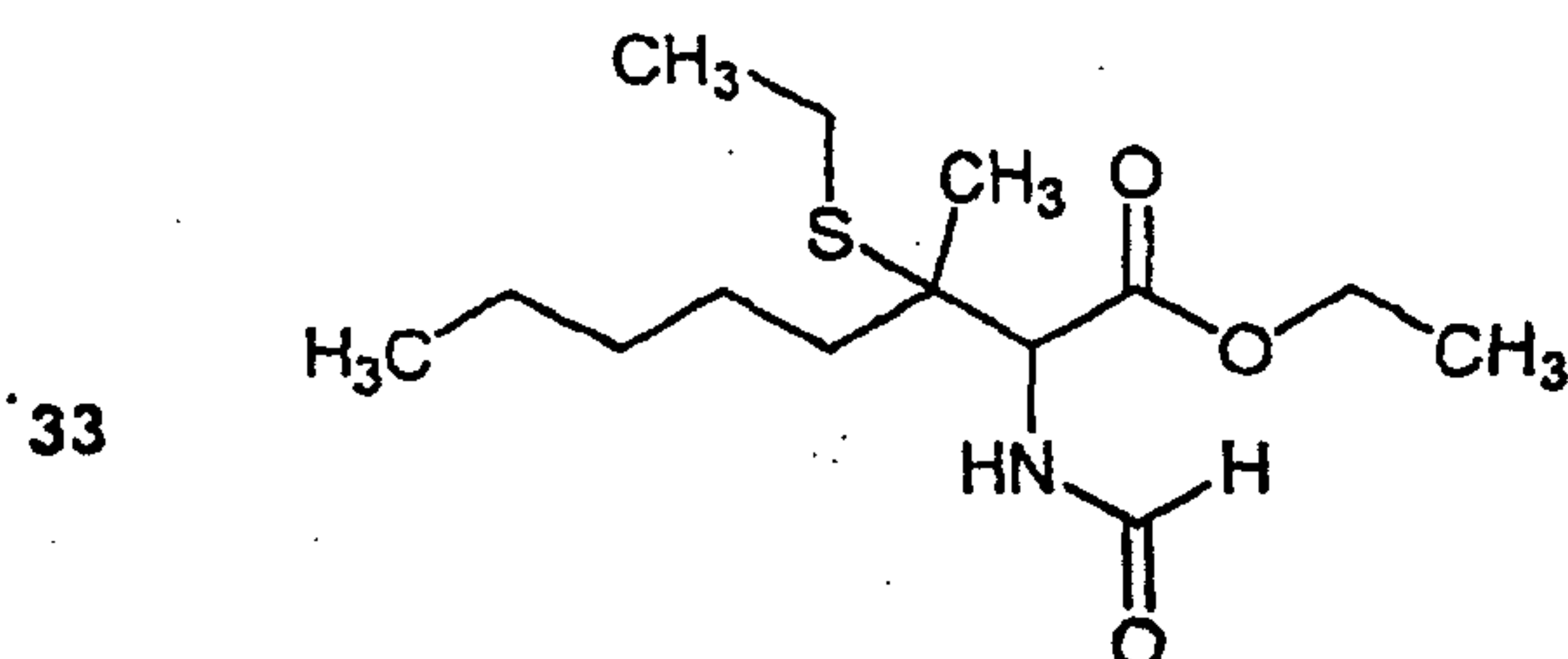
10 M/z [%] = 351 (M^+ , 1), 324 ($M^+ - \text{C}_2\text{H}_5$, 1), 306 ($M^+ - \text{C}_2\text{H}_5\text{OH}$ -1, 1), 278 ($M^+ - 73$, 1), 250 ($M^+ - \text{HCO}_2\text{Et} - \text{HCO}$, 1), 223 ($M^+ - 128$, 6), 222 ($M^+ - 129$, 17), 221 ($M^+ - \text{EtO}_2\text{CCHNHCHO}$, 100), 184 ($M^+ - 167$, 6), 91 ($M^+ - 260$, 70).

15 **Elemental analysis:**

calc.: C = 64.92 H = 8.32 N = 3.98

fd.: C = 64.50 H = 8.12 N = 4.24

20 **L) 3-Ethylsulfanyl-2-formylamino-3-methyloctanoic acid ethyl ester (33)**



$M = 289.44 \text{ g/mol}$

According to **GP 5**, 0.28 ml (0.44 mmol) of n-butyllithium,
 25 2.73 g (44 mmol) of ethyl mercaptan **36** and 1 g (4.4 mmol) of (E)-2-formylamino-3-methyl-2-octenoic acid ethyl ester **(E)-34** are reacted in 40 ml of abs. THF ($-78^\circ\text{C} \rightarrow \text{RT}$). A colourless oil is obtained, which is purified by column chromatography with DCM/ether (6:1). The product is
 30 obtained as a colourless, viscous oil.

PCT/EP01/10626

WO 02/22569

Yield: 1.05 g (36.3 mmol, 82% of theory)
de: 14% (according to ^1H - and ^{13}C -NMR)
TLC: $R_f = 0.49$ (DCM:ether - 4:1)

5

A rotameric ratio of 91:9 around the N-CHO bond is obtained.

^1H -NMR spectrum (400 MHz, CDCl_3 , diastereomer mixture):

10 δ = 8.26 (s, 0.91 H, HC=O), 8.02 (d, $J = 11.82$ + d, $J = 11.81$, 0.09 H, HC=O), 6.79 (d, $J = 9.34$ + d, $J = 8.71$, 0.91 H, HN), 6.55 (m, 0.09 H, HN), 4.77 (d, $J = 9.34$, 0.57 H, CHNH), 4.64 (d, $J = 8.71$, 0.43 H, CHNH), 4.22 (m, 2 H, OCH_2), 2.50 (m, 2 H, SCH_2), 1.43-1.73 (cz, 4H, 2 x CH_2),
 15 1.20 - 1.37 (cz, 10 H), 1.18 (tr, $J = 7.42$ + tr, $J = 7.00$, 3H, SCH_2CH_3), 0.90 (dtr, $J = 4.71$, 7.14, 3H, CH_2CH_3) ppm.

^{13}C -NMR spectrum (100 MHz, CDCl_3 , diastereomer mixture):

δ = 170.36, 170.25 (OC=O), 160.98, 160.93 (HC=O), 61.74,
 20 61.70 (OCH_2), 57.15, 57.02 (CHNH), 51.19 (SC_{quart}), 38.66, 37.86 (CH_2), 32.51, 32.42 (CH_2), 23.94 (CH_2), 23.45, 22.50 (SCCH_3), 22.90, 22.85 (CH_2), 22.17, 22.11 (CH_2), 14.44, 14.41 (OCH_2CH_3), 14.38, 14.36 (SCH_2CH_3), 14.27, 14.25 (CH_2CH_3) ppm.

25

IR-spectrum(capillary):

$\tilde{\nu}$ = 3310 (br s), 2959 (s), 2933 (vs), 2871 (s), 2929 (s), 2746 (br w), 1739 (vs, C=O), 1670 (vs, OC=O), 1513 (br s), 1460 (m), 1468 (m), 1381 (s), 1333 (m), 1298 (vw), 1262
 30 (w), 1196 (vs), 1164 (vw), 1127 (m), 1096 (m), 1070 (w), 1030 (s), 978 (w), 860 (m), 833 (m), 727 (br m) [cm^{-1}].

Mass spectrum (EI, 70 eV):

PCT/EP01/10626

WO 02/22569

M/z [%] = 289 (M^+ , 1), 260 ($M^+ - C_2H_5$, 1), 244 ($M^+ - C_2H_5OH - 1$, 1), 228 ($M^+ - SC_2H_5$, 1), 188 ($M^+ - HCO_2Et - HCO$, 1), 161 ($M^+ - 128$, 5), 160 ($M^+ - 129$, 11), 159 ($M^+ - EtO_2CCHNHCHO$, 100), 97 ($M^+ - 192$, 11), 89 ($M^+ - 200$, 11), 75 ($M^+ - 214$, 5), 55 ($M^+ - 214$, 14).

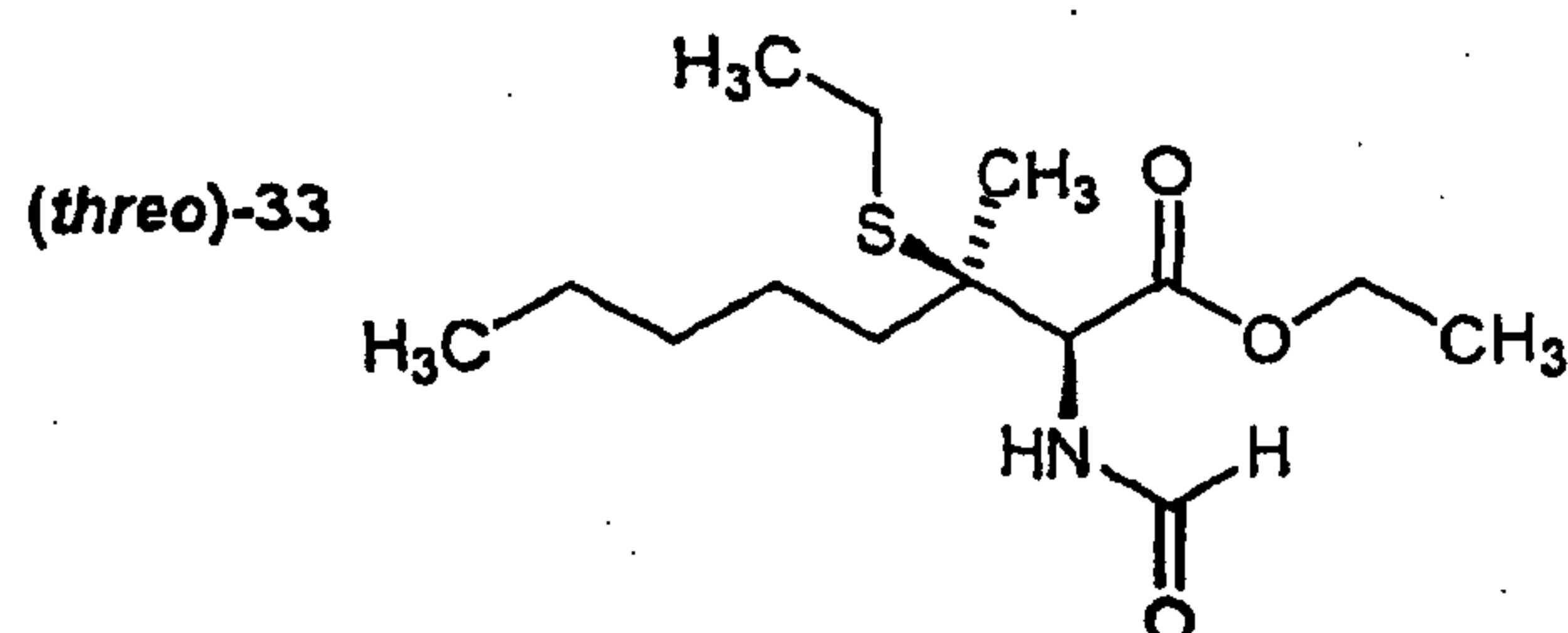
Elemental analysis:

calc.: C = 58.10 H = 9.40 N = 4.84

fd.: C = 57.97 H = 9.74 N = 5.13

10

The *threo* diastereoisomer **(threo)-33** could be obtained in elevated purity by 30 days' crystallisation in pentane/ethanol:

15 **M) threo Diastereomer ((threo)-33):**

de: 86% (according to ^{13}C -NMR)

mp: 45.5°C (colourless, crystalline)

20

A rotameric ratio of 91:9 around the N-CHO bond is obtained.

 ^1H -NMR spectrum (300 MHz, $CDCl_3$):

25 δ = 8.26, 8.01 (br s, dd, J = 11.81 H, 0.91, 0.09 H, $\underline{HC=O}$), 6.61, 6.40 (dm, J = 9.06, 0.91, 0.09 H, $\underline{HN}$), 4.77 (d, J = 9.34, 0.57 H, $\underline{CHNH}$), 4.22 (ddq, J = 7.14, 10.72, 17.79, 2 H, $\underline{OCH_2}$), 2.50 (ddq, J = 7.42, 10.72, 27.36, 2 H, $\underline{SCH_2}$), 1.42 - 1.76 (cz, 4 H, 2 x $\underline{CH_2}$), 1.24-1.38 (cz, 10 H), 1.18

PCT/EP01/10626

WO 02/22569

(dtr, $J = 3.3, 7.42, 3 \text{ H, SCH}_2\text{CH}_3$), 0.90 (tr, $J = 7.14, 3 \text{ H, CH}_2\text{CH}_3$) ppm.

^{13}C -NMR spectrum (75 MHz, CDCl_3):

5 $\delta = 170.13$ (OC=O), 160.71 (HC=O), 61.50 (OCH_2), 56.85 (CHNH), 50.97 ($\text{SC}_{\text{quart.}}$), 37.64 (CH_2), 32.22 (CH_2), 23.66 (CH_2), 23.47 (SCCH_3), 22.60 (CH_2), 21.81 (CH_2), 14.09 (OCH_2CH_3), 14.07 (SCH_2CH_3), 13.93 (CH_2CH_3) ppm.

10 **IR spectrum** (KBr pellet):

$\tilde{\nu} = 3455$ (m), 3289 (br s), 3036 (w), 2981 (s), 2933 (vs), 2860 (vs), 2829 (s), 2755 (br m), 2398 (vw), 2344 (vw), 2236 (vw), 2062 (w), 1737 (vs, C=O), 1662 (vs, OC=O), 1535 (s), 1450 (m), 1385 (s), 1373 (s), 1334 (vs), 1267 (m), 15 1201 (vs), 1154 (m), 1132 (s), 1118 (w), 1065 (m), 1050 (w), 1028 (s), 1016 (m), 978 (m), 959 (vw), 929 (w), 896 (m), 881 (m), 839 (w), 806 (m), 791 (m), 724 (s), 660 (m), 565 (m) [cm^{-1}].

20 **Mass spectrum** (Cl, isobutane):

M/z [%] = 346 ($M^+ + \text{isobutane} - 1, 2$), 292 ($M^+ + 3, 6$), 291 ($M^+ + 2, 17$), 290 ($M^+ + 1, 100$), 245 ($M^+ - \text{C}_2\text{H}_5\text{OH}, 1$), 228 ($M^+ - \text{SC}_2\text{H}_5, 6$), 159 ($M^+ - \text{EtO}_2\text{CCHNHCHO}, 8$).

25 **Elemental analysis:**

calc.: C = 58.10 H = 9.40 N = 4.84

fd.: C = 58.05 H = 9.73 N = 4.76

It has hitherto been possible to obtain diastereoisomer
30 (erythro)-33 only with a de of 50% by crystallisation of
(threo)-33; no separate analysis was performed for this.

List of abbreviations

GP	general procedure
abs.	absolute
eq.	equivalent
AcCl	acetyl chloride
Ar	aromatic
calc.	calculated
Bn	benzyl
Brine	saturated NaCl solution
BuLi	butyllithium
TLC	thin-layer chromatography
DIPA	diisopropylamine
DCM	dichloromethane
de	diastereomeric excess
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
Et	ethyl
et al.	et altera
GC	gas chromatography
fd.	found
sat.	saturated
HPLC	high pressure liquid chromatography
IR	infrared
conc.	concentrated
Lit.	literature reference
Me	methyl
min	minute
MS	mass spectroscopy
NMR	nuclear magnetic resonance
quart.	quaternary
Pr	propyl
R	organic residue

PCT/EP01/10626

WO 02/22569

RT	room temperature
bp.	boiling point
mp.	melting point
TBS	tert.-butyldimethylsilyl
Tf	triflate
THF	tetrahydrofuran
TMS	trimethylsilyl
TsOH	toluenesulfonic acid
v	volume

List of literature references

1. ^[1] D. Enders, R. W. Hoffmann, *Ch. i. u. Z.* **1985**, 19, 177.
2. ^[1] L. Pasteur, *Ann. Chim.* **1848**, 24, 442.
- 5 3. ^[1] J. A. Le Bel, *Bull Soc. Chim. Fr.* **1874**, 22, 337.
4. ^[1] J. H. van't Hoff, *Bull. Soc. Chim. Fr.* **1875**, 23, 295.
5. ^[1] T. Laue, A. Plagens, *Namen- und Schlagwort-Reaktionen der Organischen Chemie*, B. G. Teubner Verlag Stuttgart **1998**.
- 10 6. ^[1] R. Brückner, *Reaktionsmechanismen*, Spektrum Akademischer Verlag Heidelberg **1996**.
7. ^[1] E. E. Bergmann, D. Ginsburg, R. Rappo, *Org. React.* **1959**, 10, 179.
8. ^[1] T. Hudlicky, J. D. Price, *Chem. Rev.* **1989**, 89, 1467.
- 15 9. ^[1] H. Scherer, *Dissertation*, RWTH Aachen, **1991**.
10. ^[1] S. G. Pyne, P. Bloem, S. L. Chapman, C. E. Dixon, R. Griffith, *J. Org. Chem* **1990**, 55, 1086.
11. ^[1] E. S. Gubnitskaya, L. P. Peresypkina, L. I. Samarai, *Russ. Chem. Rev.* **1990**, 59, 807.
- 20 12. ^[1] T. Otten, *Dissertation*, RWTH Aachen, **2000**.
13. ^[1] D. Enders, H. Wahl, W. Bettray, *Angew. Chem.* **1995**, 107, 527.
14. ^[1] V. S. Martin, M. T. Ramirez, M. S. Soler, *Tetrahedron Lett.* **1990**, 31, 763.
- 25 15. ^[1] W. Amberg, D. Seebach, *Chem. Ber.* **1990**, 123, 2250.
16. ^[1] D. Enders, K. Heider, G. Raabe, *Angew. Chem.* **1993**, 105, 592.
17. ^[1] A. Kamimura, H. Sasatani, T. Hashimoto, T. Kawai, K. Hori, N. Ono, *J. Org. Chem.* **1990**, 55, 3437.
- 30 18. ^[1] W. D. Rudolf, R. Schwarz, *Wiss. Z.-Martin-Luther Univ. Halle-Wittenberg, Math. Naturwiss. Reihe* **1989**, 38, 25.
19. ^[1] K. Tomioka, A. Muraoka, M. Kanai, *J. Org. Chem.* **1995**, 60, 6188.

PCT/EP01/10626

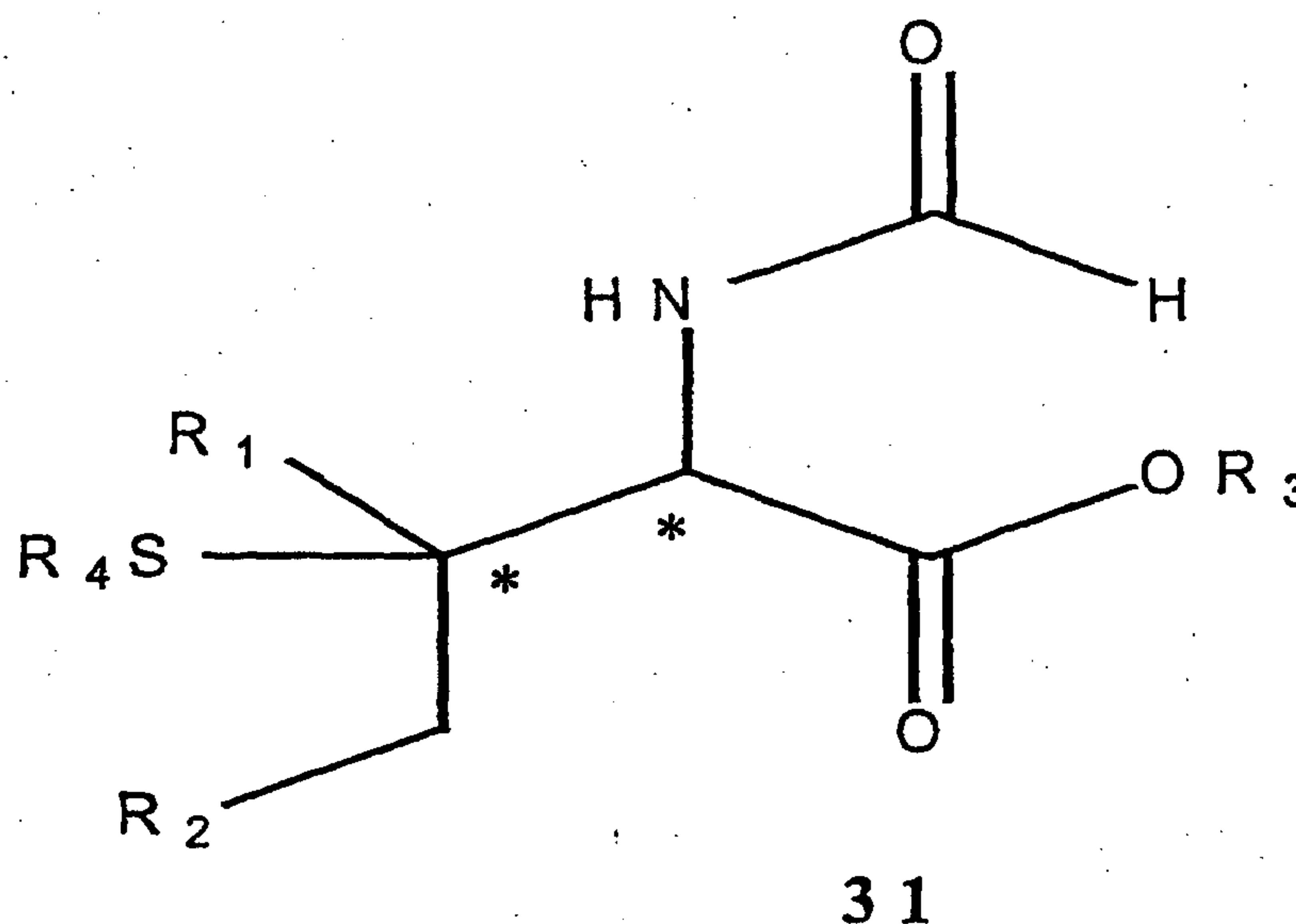
WO 02/22569

- 20.^[1] T. Naito, O. Miyata, T. Shinada, I. Ninomiya,
Tetrahedron **1997**, 53, 2421.
- 21.^[1] a) D. A. Evans, D. M. Ennis, D. J. Mathre, *J. Am.*
Chem. Soc. **1982**, 104, 1737.
- 5 b) D. A. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem.*
Soc. **1988**, 110, 1238.
- 22.^[1] A. A. Schleppnik, F. B. Zienty, *J. Org. Chem.* **1964**,
39,1910.
- 23.^[1] T. Mukaiyama, K. Suzuki, I. Ikegawa, *Bull. Chem. Soc.*
10 *Jpn.* **1982**, 55, 3277.
- 24.^[1] CD Römpp Chemie Lexikon - Version 1.0, Stuttgart/New
York: Georg Thieme Verlag **1995**.
- 25.^[1] A. Kumar, R. V. Salunkhe, R. A. Rane, S. Y. Dike, *J.*
Chem. Soc., Chem. Commun. **1991**, 485.
- 15 26.^[1] H. Wynberg, H. Hiemstra, *J. Am. Chem. Soc.* **1981**, 103,
417.
- 27.^[1] T. Mukaiyama, T. Izawa, K. Saigo, H. Takei, *Chem.*
Lett. **1973**, 355.
- 28.^[1] D. A. Evans, M. C. Willis, J. N. Johnston, *Org. Lett.*
20 **1999**, 1, 865.
- 29.^[1] S. Kanemasa, Y. Oderaotoshi, E. Wada, *J. Am. Chem.*
Soc. **1999**, 121, 8675.
- 30.^[1] B. L. Feringa, E. Keller, N. Veldman, A. L. Speck,
Tetrahedron Asymmetry **1997**, 8, 3403.
- 25 31.^[1] M. Shibasaki, T. Arai, H. Sasai, *J. Am. Chem. Soc.*
1998, 120, 4043.
- 32.^[1] K. Tomioka, *Synthesis* **1990**, 541.
- 33.^[1] K. Tomioka, K. Nishimura, M. Ono, Y. Nagaoka, *J. Am.*
Chem. Soc. **1997**, 119, 12974.
- 30 34.^[1] K. Tomioka, M. Shindo, K. Koga, *J. Org. Chem.* **1998**,
63, 9351.
- 35.^[1] C. H. Wong, W. K. C. Park, M. Auer, H. Jasche, *J. Am.*
Chem. Soc. **1996**, 118, 10150.
- 36.^[1] I. Ugi, R. Obrecht, R. Herrmann, *Synthesis* **1985**, 400.

- 37.^[1] I. Ugi, U. Fetzer, U. Eholzer, H. Knupper, K. Offermann, *Angew. Chem.* **1965**, 11, 492.
- 38.^[1] I. Maeda, K. Togo, R. Yoshida, *Bull. Chem. Soc. Jpn.* **1971**, 44, 1407.
- 5 39.^[1] U. Schöllkopf, R. Meyer, *Liebigs Ann. Chem.* **1981**, 1469.
- 40.^[1] U. Schöllkopf, R. Meyer, *Liebigs Ann. Chem.* **1977**, 1174.
- 10 41.^[1] U. Schöllkopf, F. Gerhart, R. Schröder, *Angew. Chem.* **1969**, 87, 701.
- 42.^[1] U. Schöllkopf, F. Gerhart, R. Schröder, D. Hoppe, *Liebigs Ann. Chem.* **1972**, 766, 1174.
- 43.^[1] R. K. Olsen, A. Srinivasan, K. D. Richards, *Tetrahedron Lett.* **1976**, 12, 891.
- 15 44.^[1] T. Naito, O. Miyata, T. Shinada, I. Ninomiya, T. Date, K. Okamura, S. Inagaki, *J. Org. Chem.* **1991**, 56, 6556.
- 45.^[1] D. N. Reinhoudt, V. van Axel Castelli, A. Dalla Cort, L. Mandolini, L. Schiaffino, *Chem. Eur. J.* **2000**, 6, 1193.
- 20 46.^[1] D. Enders, B. B. Lohray, *Angew. Chem.* **1987**, 99, 360.
- 47.^[1] D. Enders, B. B. Lohray, *Angew. Chem.* **1988**, 100, 594.
- 48.^[1] *Beilstein* **4**, I, 342.
- 49.^[1] R. G. Jones, *J. Am. Chem. Soc.* **1949**, 71, 644.
- 25 50.^[1] I. Maeda, K. Togo, R. Yoshida, *Bull. Chem. Soc. Jpn.* **1971**, 44, 1407.

Claims

1. A process for the production of a compound of the general formula 31



in which

R1, R2 and R3 are mutually independently selected from among

C₁₋₁₀ alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; and

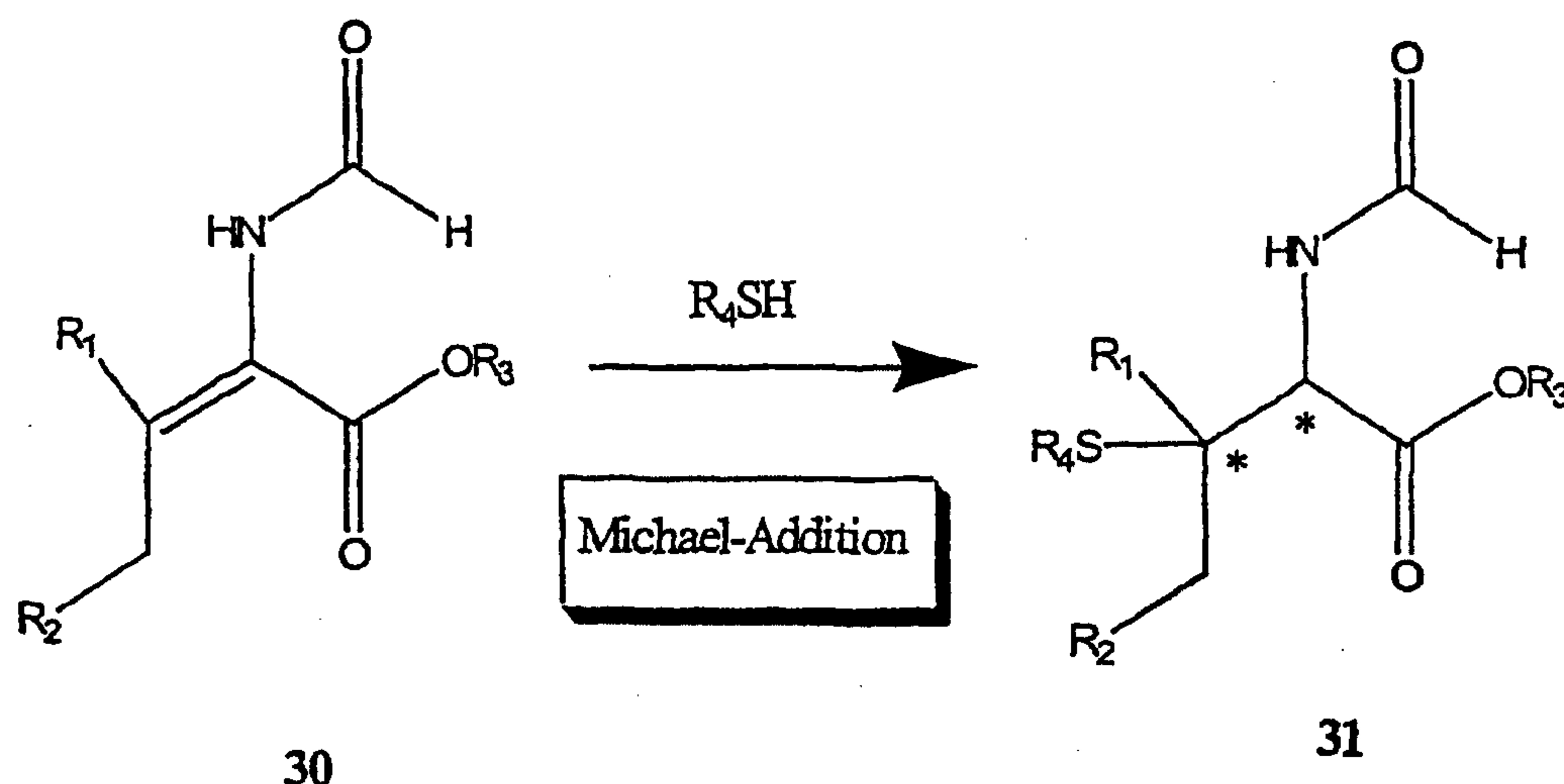
* indicates a stereoselective centre,

R4 is selected from among:

C₁₋₁₀ alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; C₃₋₈ cycloalkyl, saturated or unsaturated, unsubstituted or mono- or polysubstituted; aryl or heteroaryl, in each case unsubstituted or mono- or polysubstituted; or aryl, C₃₋₈ cycloalkyl or

heteroaryl, in each case unsubstituted or mono- or polysubstituted, attached via saturated or unsaturated C1-3 alkyl;

- 5 in which a compound of the general formula 30, is reacted under *Michael* addition conditions with a compound of the general formula R_4SH , in accordance with reaction I below:



10

Reaction I

15

20

wherein the compounds of the formula R_4SH are used as lithium thiolates or are converted into lithium thiolates during or before reaction I and/or chiral catalysts, selected from among: chiral auxiliary reagents, in particular the diether (S,S)-1,2-dimethoxy-1,2-diphenylethane; Lewis acids and/or Brønsted bases or combinations thereof are used, and are optionally then hydrolysed with bases, in particular NaOH, and optionally purified, preferably by column chromatography.

2. A process according to claim 1, characterised in that the compounds of the formula R_4SH are used as lithium

thiolates or are converted into lithium thiolates during or before reaction I.

3. A process according to one of claims 1 or 2,
5 characterised in that butyllithium (BuLi) is used before reaction I to convert the compounds of the formula R_4SH into lithium thiolates, preferably in an equivalent ratio of BuLi: R_4SH of between 1:5 and 1:20, in particular 1:10, and is reacted with R_4SH and/or the
10 reaction proceeds at temperatures of $\leq 0^\circ C$ and/or in an organic solvent, in particular toluene, ether, THF or DCM, especially THF.
4. A process according to one of claims 1 to 3,
15 characterised in that, at the beginning of reaction I, the reaction temperature is at temperatures of $\leq 0^\circ C$, preferably at between -70 and $-80^\circ C$, in particular $-78^\circ C$, and, over the course of reaction I, the temperature is adjusted to room temperature or the
20 reaction temperature at the beginning of reaction I is at temperatures of $\leq 0^\circ C$, preferably at between -30 and $-20^\circ C$, in particular $-25^\circ C$, and, over the course of reaction I, the temperature is adjusted to between $-20^\circ C$ and $-10^\circ C$, in particular $-15^\circ C$.
- 25 5. A process according to one of claims 1 to 4, characterised in that reaction I proceeds in an organic solvent, preferably toluene, ether, THF or DCM, in particular in THF, or a nonpolar solvent, in
30 particular in DCM or toluene.
6. A process according to one of claims 1 to 5, characterised in that the diastereomers are separated after reaction I, preferably by preparative HPLC or

crystallisation, in particular using the solvent pentane/ethanol (10:1) and cooling.

7. A process according to one of claims 1 to 6,
5 characterised in that the separation of the enantiomers proceeds before the separation of the diastereomers.
8. A process according to one of claims 1 to 7,
10 characterised in that R^1 means C_{1-6} alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; and R^2 means C_{2-9} alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted,
15 preferably
- R^1 means C_{1-2} alkyl, mono- or polysubstituted or unsubstituted, in particular methyl or ethyl and R^2
20 means C_{2-9} alkyl, preferably C_{2-7} alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted, in particular ethyl, propyl, n-propyl, i-propyl, butyl, n-butyl, i-butyl, tert.-butyl, pentyl, hexyl or heptyl;
25 in particular
- residue R^1 means methyl and R^2 means n-butyl.
- 30 9. A process according to one of claims 1 to 8, characterised in that R^3 is selected from among C_{1-3} alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted, preferably methyl or ethyl.

10. A process according to one of claims 1 to 9,
characterised in that R^4 is selected from among C_{1-6}
alkyl, saturated or unsaturated, branched or
5 unbranched, mono- or polysubstituted or unsubstituted;
phenyl or thiophenyl, unsubstituted or monosubstituted
(preferably with OCH_3 , CH_3 , OH , SH , CF_3 , F , Cl , Br
or I); or phenyl attached via saturated CH_3 ,
unsubstituted or monosubstituted (preferably with OCH_3 ,
10 CH_3 , OH , SH , CF_3 , F , Cl , Br or I);

R^4 is preferably selected from among C_{1-6} alkyl,
saturated, unbranched and unsubstituted, in particular
methyl, ethyl, propyl, n-propyl, i-propyl, butyl, n-
15 butyl, i-butyl, tert.-butyl, pentyl or hexyl; phenyl
or thiophenyl, unsubstituted or monosubstituted
(preferably with OCH_3 , CH_3 , OH , SH , CF_3 , F , Cl , Br
or I); or phenyl attached via saturated CH_3 ,
unsubstituted or monosubstituted (preferably with OCH_3 ,
20 CH_3 , OH , SH , CF_3 , F , Cl , Br or I),

in particular R^4 is selected from among methyl, ethyl
or benzyl, unsubstituted or monosubstituted
(preferably with OCH_3 , CH_3 , OH , SH , CF_3 , F , Cl , Br
25 or I).

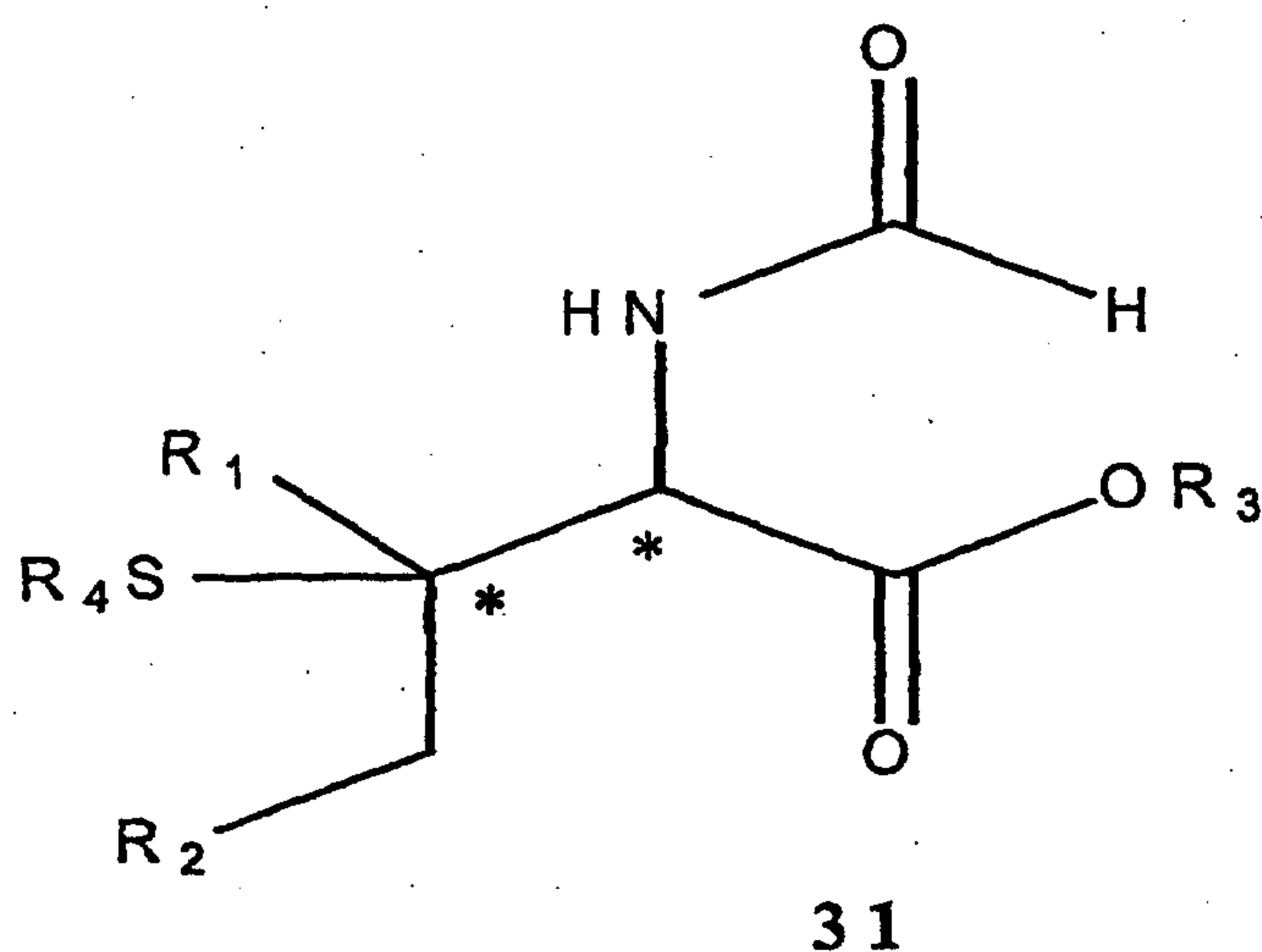
11. A process according to one of claims 1 to 10,
characterised in that the thiolate is used
stoichiometrically, $TMSCl$ is used and/or a chiral
30 proton donor R^*-H is then used,

or

that compound 30 is modified before reaction I with a sterically demanding (large) group, preferably TBDMS.

12. A process according to one of claims 1 to 11,
 5 characterised in that the compound of the general formula 31 is 3-ethylsulfanyl-2-formylamino-3-methyloctanoic acid ethyl ester or 3-benzylsulfanyl-2-formylamino-3-methyloctanoic acid ethyl ester, the compound of the general formula 30 is 2-formylamino-3-methyl-2-octenoic acid ethyl ester and R₄SH is ethyl mercaptan or benzyl mercaptan.

13. A compound of the general formula 31



15 in which

R₁, R₂ and R₃ are mutually independently selected from among C₁₋₁₀ alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted
 20 or unsubstituted;

* indicates a stereoselective centre, and

R⁴ is selected from among:

25

- 5 C₁₋₁₀ alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; C₃₋₈ cycloalkyl, saturated or unsaturated, unsubstituted or mono- or polysubstituted; aryl or heteroaryl, in each case unsubstituted or mono- or polysubstituted; or aryl, C₃₋₈ cycloalkyl or heteroaryl, in each case unsubstituted or mono- or polysubstituted, attached via saturated or unsaturated C₁₋₃ alkyl;
- 10 in the form of the racemates, enantiomers, diastereomers thereof, in particular mixtures of the enantiomers or diastereomers thereof or of a single enantiomer or diastereomer; in the form of their
- 15 physiologically acceptable acidic and basic salts or salts with cations or bases or with anions or acids or in the form of the free acids or bases.
14. A compound according to claim 13, characterised in
- 20 that R¹ means C₁₋₆ alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; and R² means C₂₋₉ alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted,
- 25 preferably
- R¹ means C₁₋₂ alkyl, mono- or polysubstituted or unsubstituted, in particular methyl or ethyl and R²
- 30 means C₂₋₉ alkyl, preferably C₂₋₇ alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted, in particular ethyl, propyl, n-propyl, i-propyl, butyl, n-butyl, i-butyl, tert.-butyl, pentyl, hexyl or heptyl;

in particular

residue R^1 means methyl and R^2 means n-butyl.

5

15. A compound according to one of claims 13 or 14,
characterised in that R^3 is selected from among C_{1-3}
alkyl, saturated or unsaturated, branched or
unbranched, mono- or polysubstituted or unsubstituted;
10 preferably methyl or ethyl.

16. A compound according to one of claims 13 to 15,
characterised in that R^4 is selected from among C_{1-6}
alkyl, saturated or unsaturated, branched or
15 unbranched, mono- or polysubstituted or unsubstituted;
phenyl or thiophenyl, unsubstituted or monosubstituted
(preferably with OCH_3 , CH_3 , OH , SH , CF_3 , F , Cl , Br
or I); or phenyl attached via saturated CH_3 ,
unsubstituted or monosubstituted (preferably with OCH_3 ,
20 CH_3 , OH , SH , CF_3 , F , Cl , Br or I);

R^4 is preferably selected from among C_{1-6} alkyl,
saturated, unbranched and unsubstituted, in particular
methyl, ethyl, propyl, n-propyl, i-propyl, butyl, n-
25 butyl, i-butyl, tert.-butyl, pentyl or hexyl; phenyl
or thiophenyl, unsubstituted or monosubstituted
(preferably with OCH_3 , CH_3 , OH , SH , CF_3 , F , Cl , Br
or I); or phenyl attached via saturated CH_3 ,
unsubstituted or monosubstituted (preferably with OCH_3 ,
30 CH_3 , OH , SH , CF_3 , F , Cl , Br or I),

in particular R^4 is selected from among methyl, ethyl
or benzyl, unsubstituted or monosubstituted

PCT/EP01/10626

WO 02/22569

(preferably with OCH₃, CH₃, OH, SH, CF₃, F, Cl, Br or I).

17. A compound according to one of claims 13 to 16,
5 characterised in that the compound is selected from among

- 3-ethylsulfanyl-2-formylamino-3-methyloctanoic acid ethyl ester or
- 10 • 3-benzylsulfanyl-2-formylamino-3-methyloctanoic acid ethyl ester.

Fetherstonhaugh & Co.
Ottawa, Canada
Patent Agents

