Asymmetric Imine Isomerisation in the Enantioselective Synthesis of Chiral Amines from Prochiral Ketones
Willems, Johannes G.H.; Vries, Johannes G. de; Nolte, Roeland J.M.; Zwanenburg, Binne

Published in:
Tetrahedron Letters

DOI:
10.1016/0040-4039(95)00641-O

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
1995

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Asymmetric Imine Isomerisation in the Enantioselective Synthesis of Chiral Amines from Prochiral Ketones

Johannes G.H. Willems¹, Johannes G. de Vries², Roeland J.M. Nolte¹ and Binne Zwanenburg¹*

¹) Department of Organic Chemistry, NSR Center for Molecular Structure, Design and Synthesis, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands
²) DSM Research B.V., Department of Fine Chemicals / Intermediates, P.O. box 18, 6160 MD Geleen, The Netherlands.

Abstract: An asymmetric catalytic synthesis of chiral amines using a chiral base catalysed [1,3]-proton shift reaction of imines is described. The isomerisation reaction of N-benzylimines 2a-b derived from prochiral ketones (benzylacetone, acetophenone) and p-substituted benzylamines, is catalysed by chiral alcohols and aminoalcohols 5-12 and gives enantiomerically enriched (up to 44% e.e.) N-benzylidene derivatives 3a-b. The resulting products 3a-b are readily hydrolysed to their corresponding amines 4a-b.

One of the synthetic approaches towards optically active amines is the asymmetric reductive amination of a prochiral ketone. Until now only a limited number of examples have been reported involving the enantioselective hydrogenation of imines (e.e.’s up to 98%), although the resulting chiral amines are important intermediates for pharmaceutical products and have found use as resolving agents. An alternative route towards optically active amines using imine intermediates is the asymmetric [1,3]-proton shift imine isomerisation by chiral bases as depicted in scheme 1. This imine isomerisation reaction (methylene azomethine rearrangement), was extensively studied by Ingold et al.² in the 1930s and by Cram et al.³ in the 1960-70s using achiral bases.

In this letter we report our preliminary results concerning the enantioselective [1,3]-proton transfer in the azaallylic system of N-benzylimines 2a-b catalysed by chiral bases (5-12) which results in the formation of thermodynamically favoured N-benzylidene derivatives 3a-b.

Scheme 1

We have checked the catalytic abilities of several chiral alcoholates in this reaction, namely those derived from (-)-N-methylephedrine (5), (-)-N-tritylephedrine (6), (2S)-N-trityl-aziridine diphenylcarbinol (7), quinine (8), quinidine (9), L(-)-menthol (10), L(-)-8-phenylmenthol (11) and L(-)-borneol (12) (Figure 1).

All imine isomerisation reactions were performed in THF or toluene in the presence of 30 mol % of chiral alcoholate catalyst. These chiral catalysts were obtained by treatment of the corresponding alcohols 5-12 with 1 equiv. of KH in THF or toluene for 60 min. at 70°C. Subsequently the imine substrates were added. The reactions were monitored using GLC and HPLC and the percentage of conversion and the e.e.’s were...
determined during the imine isomerisation process. It was found that in the case of imine 2a, derived from benzylacetone and p-chloro-benzylamine, almost no racemisation of the imine product 3a occurred under the reaction conditions applied. (Figure 2).

However, during the asymmetric isomerisation of imine 2b, derived from acetophenone and benzylamine, initial e.e.'s were also the maximum values, because during the reversible imine isomerisation process racemisation of the product 3b took place (Figure 3).

The imine isomerisation reaction can be described by first order equilibrium kinetics and k\textsubscript{overall}, k\textsubscript{1} and k\textsubscript{-1}-values could be determined from the collected data. Typical examples of a conversion versus time and e.e. versus time plot for the asymmetric imine isomerisation of 2a and 2b using the potassium alcoholate derived from 7 in toluene as the catalysts are shown in Figures 2-3. Comparison of the imine isomerisation reaction of imines 2a and 2b, using the same solvent and chiral amino alcoholate catalyst 7, shows that the isomerisation reaction of imine 2b is much faster than that of imine 2a. In the case of 2a it was necessary to heat the reaction mixture to 105°C because at lower temperatures only a low conversion of 2a into 3a occurred.

The reason for this slower isomerisation reaction of 2a in comparison with 2b is possibly due to the fact that imine 2b is able to form a more stable aza-allyl anion intermediate than imine 2a. The chiral potassium
alcoholate catalysts 5-9 were effective in catalysing the transformation of 2a-b to 3a-b. The chiral potassium alcoholates derived from 10-12 gave imine isomerisation reactions for imines 2a-b in THF and toluene, but the e.e.'s were very low (0-3%) (Table 1). From these results it was concluded that chiral alcohols are not the catalysts of choice in the asymmetric imine isomerisation reaction.

When Li⁺ and Na⁺ were used instead of K⁺ counterions no imine isomerisation reaction occurred.

Comparison of the inducing ability of the catalysts using different solvents under otherwise similar reaction conditions showed that in most cases higher e.e.'s were obtained in toluene than in THF (Table 1), but in all cases the reaction rate was lowered in toluene (Table 1). The highest e.e.'s (22-44%, entries 4-5) were observed for the isomerisation of imine 2a using the potassium alcoholate derived from 7 as the chiral base in toluene as the solvent (Figure 2). Carbinol 7 was synthesised in a 4 step procedure starting from L-Serine. The trityl group in catalyst 7 was considered of importance and therefore (-)-N-tritylephedrine (6) was synthesised starting from commercially available (-)-ephedrine. The maximum e.e.'s in the isomerisation of 2b using amino-alcohols derived from 6 and 7 were of the same order (14%, entries 13-14).

**Figure 3.** Asymmetric imine isomerisation of imine 2b using chiral potassium alcoholate derived from 7.

\[
\frac{[A]}{[A_0]} = \left(\frac{100 - \text{conversion}(%)}{100}\right) \text{ measured by GLC and } \alpha \text{ e.e } (\%) = \text{ enantiomeric excess of } 3b \text{ measured by HPLC as a function of time. Reaction conditions: } [\text{imine } 2b] = 0.2 \text{ mmol/mL, } [\text{catalyst 7}] = 0.06 \text{ mmol/mL (0.3 equiv), solvent: toluene, temperature: } 22°C.
\]

However, isomerisation of imine 2a using the alcoholate catalyst derived from (-)-N-tritylephedrine (6) led to a much lower e.e. than the imine isomerisation with the alcoholate from 7. Apparently, the enantioselectivity is both substrate and catalyst dependent.

When isomerisation reactions of imine 2b were performed in THF at room temperature a fast reaction took place and no asymmetric induction of the product imine was observed. Changing from THF to toluene using the same chiral alcoholate bases (5-10), slowed down the imine isomerisation reaction, as was also observed for imine 2a, and in all cases the reaction proceeded in an asymmetric fashion (e.e. = 2-14%, entries 12-16).

The crude product mixtures of imines 2a-b and 3a-b were hydrolysed after equilibrium was reached using 2M sulphuric acid, and the product amines 4a-b together with the p-substituted benzylamines were isolated using acid-base extraction in good yields (85-95%). The crude product mixtures were not purified but analysed by NMR, IR and GC/MS as such. After hydrolysis the e.e. of the crude amine 4a (entry 4) was checked by GLC (Mosher acid chloride derivative) and HPLC (benzaldehyde derived imine derivative) using a chiral column (Chiralpak AD). The e.e. of amine 4a, obtained after hydrolysis of 3a, was identical with the e.e. of imine 3a before hydrolysis (Figure 2), implying that no racemisation had occurred during the hydrolysis and work-up
procedure. For amine 4b (entry 14) the same procedure as described for 4a was followed, yielding an amine product 4b that had been racemised under the imine isomerisation reaction conditions applied. (Figure 3).

In conclusion, we have developed a general method for the catalytic asymmetric synthesis of chiral amines via a [1,3]-proton transfer reaction. Soloshonok et al. recently described the asymmetric isomerisation⁶ of imines derived from β-polyfluoroalkyl-β-ketocarboxylic esters and benzylamine, a special class of imines, using (+)-cinchonidine as the base in solvent free reaction conditions and high temperatures. Since their procedure can only be applied in the case of imines derived from β-keto-esters, we believe that our method is more generally applicable in the asymmetric [1,3]-proton shift reaction.

**Table 1.** Asymmetric imine isomerisation using chiral potassium alcoholates derived from 5-12

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>Reaction Conditionsᵃ</th>
<th>t₁/₂ minᵇ</th>
<th>e.e.⁹ (‰)ᶜ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(1a) PhCH₂CH₂</td>
<td>5</td>
<td>THF</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>(1a) PhCH₂CH₂</td>
<td>5</td>
<td>toluene</td>
<td>105</td>
</tr>
<tr>
<td>3</td>
<td>(1a) PhCH₂CH₂</td>
<td>6</td>
<td>toluene</td>
<td>105</td>
</tr>
<tr>
<td>4</td>
<td>(1a) PhCH₂CH₂</td>
<td>7</td>
<td>THF</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>(1a) PhCH₂CH₂</td>
<td>7</td>
<td>toluene</td>
<td>105</td>
</tr>
<tr>
<td>6</td>
<td>(1a) PhCH₂CH₂</td>
<td>8</td>
<td>THF</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>(1a) PhCH₂CH₂</td>
<td>9</td>
<td>THF</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>(1a) PhCH₂CH₂</td>
<td>10ᵈ</td>
<td>THF</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>(1a) PhCH₂CH₂</td>
<td>10</td>
<td>toluene</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>(1a) PhCH₂CH₂</td>
<td>11ᵉ</td>
<td>THF</td>
<td>66</td>
</tr>
<tr>
<td>11</td>
<td>(1a) PhCH₂CH₂</td>
<td>12ᶠ</td>
<td>THF</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>(1b) Ph</td>
<td>5</td>
<td>toluene</td>
<td>20</td>
</tr>
<tr>
<td>13</td>
<td>(1b) Ph</td>
<td>6</td>
<td>toluene</td>
<td>20</td>
</tr>
<tr>
<td>14</td>
<td>(1b) Ph</td>
<td>7</td>
<td>toluene</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>(1b) Ph</td>
<td>8</td>
<td>toluene</td>
<td>20</td>
</tr>
<tr>
<td>16</td>
<td>(1b) Ph</td>
<td>10ᵍ</td>
<td>toluene</td>
<td>20</td>
</tr>
</tbody>
</table>

a) Concentration of potassium salt of catalysts 5-12 is 30 mol % and concentration of imine is 0.2 mmol/mL. b) The parameter t₁/₂ is the reaction time for 50% conversion of the starting material. c) e.e. of 3a-b determined by HPLC (Daicel Chiralpak AD) (eluent: hexane / 2-propanol = 98 : 2, v/v). d) [10] = 60 mol %. e) [11] = 20 mol %. f) [12] = 95 mol %. g) D(+)-menthol was used.

**Acknowledgement.** We are grateful to DSM Research for their financial support. We thank Dr. A.L.L. Duchateau (DSM Research) for the development of an HPLC method for the determination of the enantiomeric purity of the imines.

**References and Notes**


4. HPLC analysis was performed on the crude imine reaction samples after quenching with 50% NaOH / ether using a Daicel Chiralpak AD Column (elucent: hexane / 2-propanol = 98:2, v/v).


(Received in UK 2 February 1995; revised 31 March 1995; accepted 7 April 1995)