Enantiotopic Desymmetrization of a Cyclic endo-Peroxide by Asymmetric Dialkylzinc Addition

Robert Ernst Ziegert, Stefan Bräse*
Institut für Organische Chemie, Universität Karlsruhe (TH), Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany
Fax +49(721)6088581; E-mail: braese@ioc.uka.de
Received 12 April 2006

Abstract: The desymmetrization reaction is a common strategy to synthesize complex chiral molecules. The selective cleavage of carbon–carbon or carbon–heteroatom bonds is well known, whereas the enantioselective cleavage of heteroatom–heteroatom bonds has been used less extensively. We demonstrate the enantiotopic addition of dialkyl zinc reagents to a bicyclic endo-peroxide using chiral [2.2]paracyclophane-based N,O-ligands as a new approach to chiral 4-alkoxy-substituted cyclohexenones.

Key words: desymmetrization, peroxide, asymmetric addition, dialkyl zinc, Michael acceptors

The desymmetrization of molecules, containing both a plane of symmetry as well as stereogenic centers (meso-compounds), is one of the most common approaches to produce semicrystal or even enantiomerically pure materials. For enantiotopic desymmetrization of molecules with carbon–carbon or carbon–heteroatom single (Figure 1, A) or multiple bonds, a number of chemical reactions,1 or enantioselective enzymatic reactions exists.2 The enantiotopic desymmetrization of molecules by cleavage of heteroatom–heteroatom bonds has been described less extensively (Figure 1, B).3a,3b

The catalytic asymmetric preparation of alcohols or amines by addition of organometallic reagents to respective C=N or C=O bonds, is one of the most important reactions in homogeneous catalysis.4 Despite numerous efforts to control the stereoselectivity of this reaction by either chiral auxiliaries1a,1b or (stoichiometric) chiral ligands,1d an extension of catalytic asymmetric addition to endo-peroxides has not been achieved (Figure 1, B).

Schwaebe and Little described the uncatalyzed addition of dialkyl zinc and other organometallic reagents to cyclic endoperoxides at low temperatures.5 An asymmetric variant is still unknown. This reaction is particularly useful for the synthesis of chiral cyclic diols. Although these endo-peroxides are important building blocks in natural product chemistry,6 their enantioselective synthesis remains somewhat cumbersome.7 Inherent difficulty of an asymmetric ligand-based addition is posed by its rapid uncatalyzed background reaction.8 Therefore, the ligand system requires high reactivity even at low temperature.

We present our results for an enantiotopic addition of dialkyl zinc reagents to cyclic endo-peroxide 8 in the presence of catalytic amounts of N,O-ligands 1–3 and 4–6 (Figure 2).9 These ligands are proved to be highly active due to their diminishing tendency to dimerize.10 Upon screening at various reaction conditions, the influences of solvent, temperature, catalyst loading and nature of the ligand were determined.11

![Figure 1](image_url) Desymmetrization of epoxides and endo-peroxides

Figure 2 [2.2]Paracyclophane-based ketimine ligands

At the outset of our study, we examined the reactivity of zinc reagents with the cyclic endo-peroxide 8, which is readily obtainable from an one-pot synthesis starting from 1,3-cyclohexadiene (7) and singlet oxygen (Scheme 1, Table 1). The reaction conditions were optimized for a bicyclic endo-peroxide, based on the protocols of Kaneko, Matsumoto and Steliou.12 A 9:1 mixture of dichloromethane and methanol with a reaction temperature of 5 °C proved to be the most effective conditions. The peroxide 8 can be obtained in an isolated yield of 71% on gram scale.

An addition reaction with two equivalents of diethyl zinc to this substrate 8 proceeded cleanly in toluene to give the monoalkylated cyclohexenediol 9-Et as the major product. To determine the enantiomeric excess, alcohol
CH₂Cl₂–MeOH (9:1) r.t. 33 a

–60 °C, an enantiomeric excess of 48% was observed with
density of the asymmetric introduction increased. At
the yield increased slightly. At lower temperature, the ten-
as reaction product.9a,9b,9d,14

excellent selectivity, but lead to the different enantiomer
all other reactions, both diastereomers exhibited good to
whereas the other diastereomer showed no selectivity. In
paracyclophane ligands induced an asymmetric induction,
This is the first example, that one diastereomer of the
(30% ee) was achieved with (R)-dimethylamine
induction could be observed. An asymmetric induction
could be effectuated with the
ligand/diethyl zinc solution to peroxide at –60 °C before
warming the mixture to 0 °C within 20 hours showed an
increase in yield to 42% but a minimal drop in selectivity
at 41% ee. Even at low temperatures, no asymmetric in-
duction could be effctuated with the S,S-diastereomer
(S,S1).

9-Et was oxidized with pyridinium dichromate (PDC)
under standard conditions.13 4-Ethoxy cyclohexenone
10-Et was obtained in 90% yields.
The influence of reaction temperature on the peroxide
opening reaction was investigated initially as shown in
Table 2 (Scheme 2). The opening reaction was performed
in absence or with 10 mol% of N,N-dimethylethanolamine
as achiral or the [2.2]paracyclophane-based ketimine
ligands as chiral N,O-ligands (Figure 2). As expected,
both uncatalyzed and achiral-promoted reactions lead to a
racemic product 9-Et at 0 °C and –15 °C in moderate
yields (18–32%). Using the S,S-diastereomer (S,S1), the
yield is slightly lesser at 0 °C. Further, no asymmetric
induction could be observed. An asymmetric induction (30% ee) was achieved with (R,S1) as chiral ligand and the
yield increased slightly. At lower temperature, the tend-
cency of the asymmetric introduction increased. At
–60 °C, an enantiomeric excess of 48% was observed with
(R,S1), but the yield decreased to 32%. Addition of the
ligand/diethyl zinc solution to peroxide at –60 °C before
warming the mixture to 0 °C within 20 hours showed an
increase in yield to 42% but a minimal drop in selectivity
to 41% ee. Even at low temperatures, no asymmetric in-
duction could be effctuated with the S,S-diastereomer
(S,S1).

This is the first example, that one diastereomer of the
paracyclophane ligands induced an asymmetric induction,
whereas the other diastereomer showed no selectivity. In
all other reactions, both diastereomers exhibited good to
excellent selectivity, but lead to the different enantiomer as reaction product.9a,9b,9d,14

**Table 1** PEROXIDATION OF 1,3-CYCLOHEXADIENE (7)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (ratio)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i-PrOH</td>
<td>r.t.</td>
<td>10a</td>
</tr>
<tr>
<td>2</td>
<td>CH₃Cl2/i-PrOH  (9:1)</td>
<td>r.t.</td>
<td>10a</td>
</tr>
<tr>
<td>3</td>
<td>CH₃Cl2/i-PrOH  (9:1)</td>
<td>0</td>
<td>21b</td>
</tr>
<tr>
<td>4</td>
<td>CH₃Cl2–MeOH    (9:1)</td>
<td>r.t.</td>
<td>33a</td>
</tr>
<tr>
<td>5</td>
<td>CH₃Cl2–MeOH    (9:1)</td>
<td>5</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>CH₃Cl2–MeOH    (9:1)</td>
<td>–10</td>
<td>&lt;10b</td>
</tr>
</tbody>
</table>

*An inseparable 3:1 mixture of peroxide 8 and phenol was isolated.

**Table 2** DESYMETRIZATION OF 8 – OPTIMIZATION OF THE REACTION TEMPERATURE

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand*</th>
<th>Temp (°C)</th>
<th>Yield (%)b</th>
<th>ee (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)&lt;S&gt;/O3</td>
<td>0</td>
<td>38</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>(S)&lt;S&gt;/O3</td>
<td>0</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>(R)&lt;S&gt;/S3</td>
<td>–15</td>
<td>49</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>(S)&lt;S&gt;/S3</td>
<td>–15</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>(R)&lt;S&gt;/S3</td>
<td>–60</td>
<td>32</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>(S)&lt;S&gt;/S3</td>
<td>–60</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>(R)&lt;S&gt;/S3</td>
<td>–60; warming to 0</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>8</td>
<td>(S)&lt;S&gt;/S3</td>
<td>–60; warming to 0</td>
<td>60</td>
<td>–9</td>
</tr>
</tbody>
</table>

* For the results of the reaction without chiral ligand or with achiral ligand see ref. 11. The algebraic symbol of the ee
declare the enantiomer. The retention times of the

Hence, the following reactions were performed at a tem-
perature of –60 °C and warming to 0 °C as a compromise
between yield and selectivity. The solvent influence was
determined as shown in Table 3. It is interesting to note,
that solvent mixtures gave better yields and selectivities
than pure solvents. It was found that the peroxide 8 as
more stable in toluene (1 M solution), even for an extend-
ed period (two months). Thus toluene was used as solvent
for further reactions.

The next series of investigation was to test the influence
of the catalyst loading on selectivity. The results are
shown in Figure 3.11 The enantiomeric excess seemed to
increase to 50–55% ee. Neither the reaction time nor
the temperature entailed an increase of the selectivity. Al-
though the starting material shows reactivity with dialkyl-
zinc, the catalyzed reaction is much faster, as
demonstrated by the influence of the catalyst loading.

To further improve the reaction conditions, we sent the
endo-peroxide 8 to a ligand screening, employing [2.2]paracyclophane-based N,O-ligands depicted in
Figure 2. The results are shown in Table 4. An increase of
the selectivity could not be observed with any of the ligands beside \((R_p,S)-1\). In contrast to ligand \((R_p,S)-1\), the \(R_p,S\)-diastereomer \((R_p,S)-4\) of the benzoyl-based imine showed no selectivity (7% ee, entry 4). However, using \(4\) and the cyclohexyl-substituted ligands \(2\) and \(5\), a selectivity was not observed with the \(R_p,S\)-but with the \(S_p,S\)-diastereomers with 17–36% ee for the second enantiomer (entries 8, 10 and 11). The other paracyclophane ligands did not show selectivity. As comparison, we used prolinol \(11\) and \((–)\)-DBNE \(12\) as catalysts (Figure 4), which are known as effective N,O-ligands in various reactions. Prolinol \(11\) yielded the desired opening product \(9\)-Et in 48% and 26% ee, whereas \(12\) led to a racemic product (41% yield). Another set of reactions was performed at a constant reaction temperature of \(-60^\circ\text{C}\). We observed similar tendencies for both reactivity and selectivity. The yields decreased slightly, while the enantiomeric excesses gave a slight increase. For details, see the supporting information.\(^{11}\)

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**Table 3** Influence of the Solvent to the Selectivity\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (^b)</th>
<th>Yield (%) (^c)</th>
<th>ee (%) (^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>Toluene–CH(_2)Cl(_2)</td>
<td>37</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>Toluene–THF</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Toluene–Et(_2)O</td>
<td>74</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>CH(_2)Cl(_2)</td>
<td>67</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>Et(_2)O</td>
<td>59</td>
<td>43</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: 10 mol% \((R_p,S)-1\), \(-60^\circ\text{C}\) warming to 0 °C, 20 h.
\(^b\) Solvent mixture 1:1.
\(^c\) Isolated yields of the opening product. Yield of oxidation product 90%, see ref. 11.
\(^d\) Determined by HPLC, see ref. 11.

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**Table 4** Ligand Screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (10 mol%)</th>
<th>Yield (%) (^a)</th>
<th>ee (%) (^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>((R_p,S)-1)</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>((R_p,S)-2)</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>((R_p,S)-3)</td>
<td>32</td>
<td>–7</td>
</tr>
<tr>
<td>4</td>
<td>((R_p,S)-4)</td>
<td>34</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>((R_p,S)-5)</td>
<td>49</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>((R_p,S)-6)</td>
<td>44</td>
<td>–9</td>
</tr>
<tr>
<td>7</td>
<td>((S_p,S)-1)</td>
<td>60</td>
<td>–9</td>
</tr>
<tr>
<td>8</td>
<td>((S_p,S)-2)</td>
<td>61</td>
<td>–36</td>
</tr>
<tr>
<td>9</td>
<td>((S_p,S)-3)</td>
<td>56</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>((S_p,S)-4)</td>
<td>37</td>
<td>–17</td>
</tr>
<tr>
<td>11</td>
<td>((S_p,S)-5)</td>
<td>51</td>
<td>–27</td>
</tr>
<tr>
<td>12</td>
<td>((S_p,S)-6)</td>
<td>14</td>
<td>n.d.</td>
</tr>
<tr>
<td>13</td>
<td>11</td>
<td>48</td>
<td>26</td>
</tr>
<tr>
<td>14</td>
<td>12</td>
<td>41</td>
<td>–1</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yields of the opening product. Yield of oxidation product 90%, see ref. 11.
\(^b\) Reaction conditions: 2 equiv of Et\(_2\)Zn, toluene, \(-60^\circ\text{C}\); warming to 0 °C, 20 h.
\(^c\) Reaction conditions: PDC, CH\(_2\)Cl\(_2\), r.t., 5 h.
\(^d\) The algebraic symbol of the ee should declare the excess enantiomer. The retention times of the enantiomers are \(t_k\) (1) = 26.5 min and \(t_k\) (2) = 31.3, ee >0 denotes signal \(t_k\) (1) > signal \(t_k\) (2) and ee <0 denotes signal \(t_k\) (1) < signal \(t_k\) (2).
To determine the influence of reactivity in dialkylzinc reagents due to selectivity, diethylzinc as well as dimethyl- 
disopropyl- and dibutylzinc (Table 5) were used. How-
ever, the most reactive diethylzinc turned out to be the 
most selective reagent in this case. Contrasting to the 
reaction with diethylzinc, the \( \left( \text{S,S} \right) \)-diastereomer of 1 also 
showed a slight selectivity (−9% to 15% ee, entries 2, 4 
and 6). This indicates that the reaction of the diethylzinc/ 
\( \left( \text{S,S} \right) \)-I is faster than the \( \left( \text{R,R} \right) \)-analogue, because the 
decrease of reactivity in dialkylzinc species resulted a 
decrease in reaction rate. As result, an increase in selectivity 
was detected. None of the alkoxy-substituted cyclohex-
enones are known in enantiomerically enriched form.\(^{17}\)

### Table 5 Influence of the Dialkylzinc Reagent to the Selectivity\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>( \text{R}_2\text{Zn} )</th>
<th>Ligand (10 mol%)</th>
<th>Yield (%)(^b)</th>
<th>ee (%)(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{Me}_2\text{Zn} )</td>
<td>( \left( \text{R,R} \right) )-I</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>( \text{Me}_2\text{Zn} )</td>
<td>( \left( \text{S,S} \right) )-I</td>
<td>64</td>
<td>–14</td>
</tr>
<tr>
<td>3</td>
<td>( \text{i-Pr}_2\text{Zn} )</td>
<td>( \left( \text{R,R} \right) )-I</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>( \text{i-Pr}_2\text{Zn} )</td>
<td>( \left( \text{S,S} \right) )-I</td>
<td>27</td>
<td>–15</td>
</tr>
<tr>
<td>5</td>
<td>( \text{n-Bu}_2\text{Zn} )</td>
<td>( \left( \text{R,R} \right) )-I</td>
<td>66</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>( \text{n-Bu}_2\text{Zn} )</td>
<td>( \left( \text{S,S} \right) )-I</td>
<td>47</td>
<td>–9</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: toluene, 10 mol% ligand, –60 \(^\circ\)C; warming to 
0 \(^\circ\)C, 20 h.

\(^b\) Only the results of the asymmetric induced reaction are given. For 
results of the reaction without chiral ligand see ref. 11.

\(^c\) Isolated yields of the opening product (yield of oxidation product up to 
90\%, see ref. 11).

\(^d\) Determined by HPLC, see ref. 11.

In summary, we have demonstrated the first enantiotopic 
ligand–accelerated dialkylzinc addition to an \textit{endo}-perox-
ide. The extension of this methodology to other orga-
nozinc reagents is currently under investigation. Due to 
simplicity of the process and availability of the \textit{endo}-perox-
ide from corresponding diene, a broad application of 
the reported catalytic reaction can be anticipated. Furth-
more, the desymmetrization of bicyclic \textit{endo}-peroxides 
might set a new benchmark for ligand-catalyzed reactions of 
organozinc reagents.

### General Protocol\(^11\)

**Synthesis of the Peroxide 8**

Under an atmosphere of argon, 3.23 g (3.74 mL, 31.0 mmol) of 1,3-
cyclohexadiene (7) and 10 mol% of Rose Bengal (347 mg, 3.10 
mmol) were dissolved in a mixture of CH\(_2\)Cl\(_2\)–MeOH (600 mL, 
9:1). At 5 \(^\circ\)C, oxygen was bubbled through the solution and the 
reaction mixture was irradiated with mercury-vapor lamp (125 W) for 
6 h. The reaction mixture was stirred at the same temperature over-
night in the dark and without oxygen stream. The solvent was sep-
arated under reduced pressure. Because of peroxide stability, the 
temperature of the water bath should not exceed 40 \(^\circ\)C! Rose Ben-
gal was filtered off (100 \( \times \) 50 mm, silica, n-pentane–Et\(_2\)O, 2:1). The 
 crude product was purified by flash chromatography (200 \( \times \) 50 mm, 
silica, n-pentane–Et\(_2\)O, 2:1). The product was obtained as a color-
less solid, yield 1.70 g (49\%).

**Peroxide Opening Reaction**

a) Without Promoter

One equiv of peroxide 8 was dissolved in toluene (2 mL/mmol) and 
cooled to the given temperature. Two equiv of a solution of the 
dialkylzinc reagent were added dropwise and the mixture was stirred 
for 20 h at the same temperature. The reaction was hydrolyzed with 
a solution of HCl (1 M, 1 mL/mm Zn reagent), extracted with 
Et\(_2\)O and washed with brine. The combined organic layers were 
dried with MgSO\(_4\). The solvent was separated under reduced pres-
sure and the crude product was purified by flash chromatography 
(200 \( \times \) 20 mm, n-pentane–Et\(_2\)O, 2:1).

b) With Achiral or Chiral N,O-Ligand

The ligand was dissolved in toluene (2 mL/mmol) and 2 equiv of 
the dialkylzinc reagent solution were added. The solution was stirred 
at r.t. for 30–60 min and then added to a solution of peroxide 8 in 
toluene (2 mL/mmol) at the given temperature. After stirring for 20 h, 
the work-up was done like described above.

For the ligands with paracyclophane backbone, one protocol is 
specified exemplary for each compound.

**Oxidation of the Cyclic Alcohols**

One equiv of pyridinium dichromate (PDC) was suspended in 
CH\(_2\)Cl\(_2\) (10 mL/mmol) and stirred for 10 min. The alcohol was dis-
solved in CH\(_2\)Cl\(_2\) (1 mL) and added to the PDC suspension at r.t. 
After complete conversion (TLC control), the crude mixture was 
filtrated over silica (100 \( \times \) 20 mm, n-pentane–Et\(_2\)O, 4:1).

**Acknowledgment**

We thank the DFG [BR 1750-1, SFB 380, CFN (E1.1)] and the 
Fonds der Chemischen Industrie for financial support, Dr. Klaus 
Ditrich, BASF AG, Germany, for donation of chiral amines 
(Chipros) and Henning Vogl for assistance in HPLC measurements.

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Enantiotopic Desymmetrization of a Cyclic *endo*-Peroxide

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Synlett 2006, No. 13, 2119–2123 © Thieme Stuttgart · New York


(11) The Supporting Information containing general remarks, synthesis details, analytical details (NMR, IR, MS, HRMS, HPLC) and complete tabularic results are available from the authors.


