Lewis acid-catalyzed Diels-Alder reaction of 2-cyclopentenones with Danishefsky’s diene: double bond isomerization of tetrahydro-1H-indene-1,5(7aH)-diones, and attempts on an asymmetric catalysis

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Dedicated to Prof. Rainer Beckert on the occasion of his 60th birthday

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Abstract
This work describes the investigation of the Diels-Alder reaction of the electron-rich diene trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) and the non-activated dienophiles 2-cyclopentenone and 2-methyl-2-cyclopentenone with respect to reactivity, regioselectivity and stereoselectivity. An observed double bond isomerization limits the practicability of 2-cyclopentenone as a dienophile in Diels-Alder reactions. 2-Methyl-2-cyclopentenone could be converted quantitatively into one regioisomeric Diels-Alder adduct, however the stereochemical control turned out to be very demanding.

Keywords: Diels-Alder reaction, Danishefsky’s diene, cyclic enones, double bond isomerization

Introduction

The use of electron-rich dienes is a common method to improve both reactivity and regioselectivity in Diels-Alder [4+2] cycloadditions. Among the most prominent members of such electron-rich dienes there is Danishefsky’s diene, i.e. trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene 2 (Scheme 1), which has originally been used to prepare pyrones from aldehyde dienophiles.¹ Later Danishefsky’s diene 2 was used extensively for the formation of 6-membered carbo- and heterocycles.²⁻⁴ When diene 2 is treated with alkenes such as 1, the intermediate cycloadduct 3 can eliminate MeOH very easily so that cyclohexenones 4 become available. Besides Danishefsky’s diene 2 a variety of related electron-rich dienes 5-8 have been developed.⁵ Whereas the use of (-M)-substituted cyclopentenones in Diels-Alder reactions with
Danishefsky’s diene 2 is well explored, only few examples are known, where non-activated cyclopentenones have been employed as starting materials. Thus, we were interested in exploring the scope of [4+2] cycloadditions employing diene 2 and non-activated 2-cyclopentenone 9a and 2-methyl-2-cyclopentenone 9b with respect to reactivity, regioselectivity and possibly stereoselectivity. The results towards this goal are reported below.

\[ R \quad + \quad \text{OTMS} \quad \text{[4 + 2]} \quad \text{OMe} \quad \text{OTMS} \quad R \quad \text{OMe} \quad \text{OTMS} \quad R \quad \text{OMe} \quad \text{OTMS} \quad \text{H}^+ \]

\[ \text{Scheme 1. Diels-Alder reactions with Danishefsky’s diene and related electron-rich dienes.} \]

**Results and Discussion**

First various conditions were screened for the cycloadditions. The results are summarized in Scheme 2 and Table 1. Following a procedure by Ishikawa, a solution of 2-cyclopentenone 9a in CH₂Cl₂ was treated with 10 mol% of ZnCl₂ for 15 min at room temperature and then cooled to 0 °C. Later 1.2 equiv. of Danishefsky’s diene 2 were added and the mixture was hydrolyzed after 2 h with 1 N HCl and submitted to aqueous workup. Although GC of the reaction mixture indicated 99% conversion of the starting material 9a, only 49% of a 63:37 mixture of two inseparable products with the desired m/z 150 (entry 1) was obtained. In order to improve the amount of products, Me₂AlCl in CH₂Cl₂ at -28 °C was tested next, albeit to give only a yield of 18% and a product ratio of 56:44 (entry 5). When SnCl₄ in THF at -78 °C was employed, the GC yield improved to 54% but again with an almost equimolar mixture (43:57) of the two products (entry 7). Unfortunately, regardless of the Lewis acid or solvent tested, the product ratio and yield could not be improved very much. The cleanest reaction without accompanying decomposition products was observed for BF₃·OEt₂ in CH₂Cl₂ at 0 °C. After 5 min quantitative conversion was achieved with 59% of the two products (43:57), which could be isolated in 20% combined yield.
Scheme 2

Table 1. Diels-Alder reaction of 2-cyclopentenone 9a with Danishefsky’s diene 2 in the presence of various Lewis acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Solvent</th>
<th>Temperature [°C]</th>
<th>Time</th>
<th>Conv. [%]</th>
<th>GC-Yield [%]</th>
<th>Ratio [%]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>ZnCl₂</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>2 h</td>
<td>99</td>
<td>49</td>
<td>63 : 37</td>
<td></td>
</tr>
<tr>
<td>(2)</td>
<td>ZnCl₂</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>1 h</td>
<td>93</td>
<td>39</td>
<td>82 : 18</td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>ZnCl₂</td>
<td>toluene</td>
<td>40</td>
<td>5 min</td>
<td>100</td>
<td>46</td>
<td>33 : 67</td>
<td></td>
</tr>
<tr>
<td>(4)</td>
<td>ZnCl₂</td>
<td>THF</td>
<td>22</td>
<td>7 d</td>
<td>98</td>
<td>13 b</td>
<td>46 : 54</td>
<td></td>
</tr>
<tr>
<td>(5)</td>
<td>Me₂AlCl</td>
<td>CH₂Cl₂</td>
<td>-28</td>
<td>60 h</td>
<td>100</td>
<td>18</td>
<td>56 : 44</td>
<td></td>
</tr>
<tr>
<td>(6)</td>
<td>Me₂AlCl</td>
<td>THF</td>
<td>0</td>
<td>5 h</td>
<td>94</td>
<td>17</td>
<td>88 : 12</td>
<td></td>
</tr>
<tr>
<td>(7)</td>
<td>SnCl₄</td>
<td>THF</td>
<td>-78</td>
<td>3 h</td>
<td>100</td>
<td>54</td>
<td>43 : 57</td>
<td></td>
</tr>
<tr>
<td>(8)</td>
<td>TiCl₄</td>
<td>THF</td>
<td>-78</td>
<td>1 h</td>
<td>96</td>
<td>2 c</td>
<td>50 : 50</td>
<td></td>
</tr>
<tr>
<td>(9)</td>
<td>BF₃·OEt₂</td>
<td>THF</td>
<td>-78</td>
<td>0.5 h</td>
<td>80</td>
<td>16</td>
<td>56 : 44</td>
<td></td>
</tr>
<tr>
<td>(10)</td>
<td>BF₃·OEt₂</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>5 min</td>
<td>100</td>
<td>59</td>
<td>43 : 57</td>
<td></td>
</tr>
</tbody>
</table>

2.4 equiv. of Danishefsky’s diene were used. bBesides 10, 12 57% of 1,3,5-triacetylbenzene were detected in the GC. c58% of 1,3,5-triacetylbenzene was detected.

Initially, we surmised that the two peaks in the GC, which referred to m/z 150, were the two regioisomers 10, 11. However, the presence of almost equimolar mixtures made us suspicious that the two products might not be these regioisomers, because the frontier orbital interactions of the HOMO of Danishefsky’s diene 2 with the LUMO of 2-cyclopentenone 9a and the corresponding orbital coefficients should strongly favor regioisomer 10, i.e. the “quasi-para” product rather than the “quasi-meta” product 11. A close inspection of the NMR spectra of the mixtures, in particular the 1D ¹H-NMR and 2D HSQC and HMBC as well as ¹³C-NMR DEPT spectra, suggested that the two GC peaks refer to the two C=C bond isomers 10, 12 rather than the regioisomers 10, 11.
In order to prove this assumption, the mixture of 10, 12 was submitted to reduction of the C=C bond. Following the procedure by Mirza-Aghayan\textsuperscript{12} the mixture was treated with 10 mol\% of \( \text{PdCl}_2 \) and \( \text{Et}_3\text{SiH} \) in MeOH at 80 °C for 11 h and the resulting product was isolated in 33\% (Scheme 3). Indeed, only a single diketone 13 was obtained.

\[
\text{Scheme 3}
\]

Any attempts to separate the double bond isomers 10, 12 by chromatography were unsuccessful and therefore we studied the conversion of 10, 12 into carbonyl derivatives such as ketals or hydrazones. As shown in Scheme 4, the mixture of 10, 12 was reacted with 2 equiv. of ethylene glycol in the presence of PPTS in benzene at 100 °C under Dean-Stark conditions. After workup and purification 75\% of an inseparable mixture of monoketal 14 and diketal 15 were obtained. Comparison of the NMR spectra with the starting material 10, 12 revealed that the ketalization took exclusively place with the C6/C7 double bond isomer 10 rather than the C7/C7a isomer 12.

\[
\text{Scheme 4}
\]

The E configuration of the C=N bond of compounds 16, 17 was arbitrarily assigned.\textsuperscript{13}
Next, we were curious whether the enone 10 with the C6/C7 double bond is indeed the more reactive one. Enones 10, 12 were treated with 2 equiv. of 2,4-dinitrophenylhydrazine in the presence of H₂SO₄ in EtOH to yield 50% of a 1:1 mixture of mono- and bishydrazone 16, 17 respectively (Scheme 4). Similarly to the ketalization no trace of the hydrazones derived from the C7/C7a enone 12 was detected. The two products 16, 17 could be separated by preparative HPLC, but any attempts to remove the hydrazone moiety were unsuccessful.¹⁴

Figure 1. ¹H-NMR spectra of the inseparable C=C bond isomers 10 and 12, the ketales 14 and 15 and the hydrazones 16 and 17 in the range of 5.6 ppm and 6.5 ppm (vinylic domain).¹⁵
So far we described that C=C bond isomerization severely limits the utility of 2-cyclopentenone 9a as a dienophile and thus the following experiments were carried out with 2-methyl-2-cyclopentenone 9b. Thus 9b was treated with 1.2 equiv. of Danishefsky’s diene 2 in CH2Cl2 in the presence of 10 mol% AlCl3 at 0 °C for 1h followed by aqueous workup (Scheme 5, Table 2). The GC of the crude product contained 65% of the desired enone 18 together with decomposition products (entry 1). Even the milder Lewis acid ZnCl2 at 0 °C did not improve the yield (entry 2). Although the use of SnCl4 at -78 °C gave an increased yield (81%), product formation was accompanied by decomposition (entry 3). The utilization of BH3 as Lewis acid did not work at all. No reaction could be detected at room temperature. As in the case of 2-cyclopentenone 9a again BF3·OEt2 in CH2Cl2 at 0 °C gave the cleanest reaction and the product enone 18 could be isolated in quantitative yield. It should be noted that compound 18 represents a complementary C=C bond isomer to the famous Hajos-Wiechert ketone 19, which has been prepared by organocatalysis.16

![Scheme 5](image-url)

**Table 2.** Diels-Alder reaction of 2-methyl-2-cyclopentenone 9b with Danishefsky’s diene 2 in the presence of various Lewis acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Temperature [°C]</th>
<th>Time</th>
<th>Conv. [%]</th>
<th>GC-Yield [%]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>AlCl3</td>
<td>22</td>
<td>2 h</td>
<td>100</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>(2)</td>
<td>ZnCl2</td>
<td>0</td>
<td>1 h</td>
<td>100</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>SnCl4</td>
<td>-78</td>
<td>1 h</td>
<td>100</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>(4)</td>
<td>BH3</td>
<td>22</td>
<td>72 h</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(5)</td>
<td>ArB(OH)2 a</td>
<td>0</td>
<td>5 min</td>
<td>100</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>(6)</td>
<td>BF3·OEt2</td>
<td>0</td>
<td>5 min</td>
<td>100</td>
<td>100</td>
<td>100</td>
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</table>

aArB(OH)2 = 3,5-(CF3)2C6H3B(OH)2

Next, a variety of chiral Lewis acids 20 - 25 were tested (Scheme 6, Table 3). Surprisingly, oxazaborolidinones 20a-c and oxazaborolidines 21a-d did not catalyze the Diels-Alder reaction between 2-methyl-2-cyclopentenone 9b and Danishefsky’s diene 2 at all.17 Their activated counterparts 20a-c-Lewis acid, or 21a-d-Lewis acid,18 titanium BINOL complex 22 (Mikami’s
catalyst),\textsuperscript{19,20} or Seebach’s titanium TADDOLate complex 23 however enabled the conversion but did not produce any enantioselectivity.\textsuperscript{21} Only racemic product 18 was detected. A promising result was obtained, when the boronic ester 24\textsubscript{a}\textsuperscript{22} was employed, resulting in 81\% of the product with 20\%ee (entry 15). Recently, Nishida introduced a new axially chiral catalyst 25, which gave good yields and high ee’s with Danishefsky’s diene 2 and oxazolidinone-substituted enoates.\textsuperscript{23} Unfortunately these promising results could not be confirmed when this new BINAMIDE complex 25 was used in the asymmetric Diels-Alder reaction of 2-methyl-2-cyclopentenone 9\textsubscript{b} and Danishefsky’s diene 2, giving rise to an enantiomeric excess of 7\%.

\begin{align*}
20\text{a} & R = H \\
20\text{b} & R = n\text{-Bu} \\
20\text{c} & R = 3,5-(\text{CF}_3)\text{C}_6\text{H}_3 \\
\text{LA} & = \text{BH}_3, \text{BF}_3, \text{CF}_2\text{SO}_3\text{H} \\
21\text{a} & R_1 = R_2 = \text{Ph} \\
21\text{b} & R_1 = \text{Ph}, R_2 = 1\text{-naphthyl} \\
21\text{c} & R_1 = R_2 = 2\text{-naphthyl} \\
21\text{d} & R_1 = R_2 = \text{Me} \\
\text{LA} & = \text{AlBr}_3, \text{CF}_2\text{SO}_3\text{H} \\
\text{22} & \text{(Mikami's catalyst)}
\end{align*}

\begin{align*}
23 & \text{Cl-TiO} \\
24\text{a} & \text{Ar} = 3,5-(\text{CF}_3)\text{C}_6\text{H}_3 \\
24\text{b} & \text{Ar} = \text{Ph} \\
24\text{c} & \text{Ar} = p\text{-tolyl} \\
\text{25} & \text{Yb(OTf)}_3 \text{ (1 equiv)} \\
& \text{(S)-BINAMIDE (1.2 equiv)} \\
& \text{DBU (2.4 equiv)}
\end{align*}

\textbf{Scheme 6.} Chiral Lewis acids employed in the Diels-Alder reaction of 9\textsubscript{b} and 2.
Table 3. Diels-Alder reaction of 2-methyl-2-cyclopentenone 9b with Danishefsky’s diene 2 in the presence of chiral Lewis acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Solvent</th>
<th>Temperature [°C]</th>
<th>Time</th>
<th>Conv. [%]</th>
<th>GC-Yield [%]</th>
<th>%ee</th>
<th>Yield [%]</th>
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<tr>
<td>(1)</td>
<td>20a·BH3</td>
<td>CH2Cl2</td>
<td>-15</td>
<td>7 h</td>
<td>20</td>
<td>76</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(2)</td>
<td>20a·BF3</td>
<td>CH2Cl2</td>
<td>-78</td>
<td>1 h</td>
<td>70</td>
<td>93</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>20a·CF3SO3H</td>
<td>CH2Cl2</td>
<td>-78</td>
<td>10 min</td>
<td>70</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(4)</td>
<td>20b·BF3</td>
<td>CH2Cl2</td>
<td>-78</td>
<td>10 min</td>
<td>80</td>
<td>66</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(5)</td>
<td>20a·CF3SO3H</td>
<td>CH2Cl2</td>
<td>-78</td>
<td>10 min</td>
<td>25</td>
<td>31</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(6)</td>
<td>20c·BF3</td>
<td>CH2Cl2</td>
<td>-78</td>
<td>10 min</td>
<td>50</td>
<td>65</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(7)</td>
<td>20c·CF3SO3H</td>
<td>CH2Cl2</td>
<td>-78</td>
<td>10 min</td>
<td>25</td>
<td>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(8)</td>
<td>21a·CF3SO3H</td>
<td>CH2Cl2</td>
<td>-78</td>
<td>5 min</td>
<td>40</td>
<td>35</td>
<td>0</td>
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<tr>
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<td>21a·AlBr3</td>
<td>CH2Cl2</td>
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<td>10 min</td>
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<td>95</td>
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<td>90</td>
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<td>1 h</td>
<td>50</td>
<td>95</td>
<td>0</td>
<td>46</td>
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<tr>
<td>(11)</td>
<td>21c·AlBr3</td>
<td>CH2Cl2</td>
<td>-15</td>
<td>3 h</td>
<td>75</td>
<td>95</td>
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<td>1 h</td>
<td>50</td>
<td>65</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(13)c</td>
<td>22</td>
<td>CH2Cl2</td>
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<td>4 h</td>
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<td>70</td>
<td>0</td>
<td></td>
</tr>
<tr>
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<td>23</td>
<td>CH2Cl2</td>
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<td>2 h</td>
<td>50</td>
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<td>0</td>
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</tr>
<tr>
<td>(15)d</td>
<td>24a</td>
<td>C2H5CN</td>
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<td>5 min</td>
<td>24</td>
<td>82</td>
<td>20</td>
<td>81</td>
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<tr>
<td>(16)</td>
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<td>36 h</td>
<td>10</td>
<td>10</td>
<td>7</td>
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</table>

aCatalyst loading: 10 mol%. bYields of products after purification. c20mol% of the catalyst was used. dEnantiomeric ratio determined on a Amidex B capillary column (length: 20 m, diameter: 0.25 mm, 0.35 bar H2), initial temperature 40 °C, 1 min isothermal, heating rate 2.5 °C/min, end temperature 200 °C, R1 = 25.46 min, R2 = 26.19 min.

Conclusions

The formation of tetrahydro-1H-indeniones 10, 18 by Lewis acid-catalyzed Diels-Alder reaction of 2-cyclopentenone 9a or 2-methyl-2-cyclopentenone 9b and Danishefsky’s diene 2 was explored. The cycloaddition of 2-cyclopentenone 9a suffers from rapid C=C bond isomerization from the C6/C7 enone 10 to the C7/C7a enone 12, thus making any attempts towards an enantioselective route unsuccessful. In contrast, the reaction of 2-methyl-2-cyclopentenone 9b gave exclusively one regioisomer 18. However, the stereochemical control turned out to be very challenging, giving only 20%ee and 7%ee with the chiral Lewis acids 24 and 25 respectively, whereas all other chiral Lewis acids produced only racemic compound 18.
The results suggest that the development of novel chiral Lewis acids presumably operating via cooperative catalysis is highly desirable.

**Experimental Section**

**General.** $^1$H-NMR and $^{13}$C-NMR spectra were obtained at 300 MHz or 500 MHz and 75 MHz or 125 MHz respectively, using a Bruker Avance 300 or Avance 500 spectrometer with tetramethylsilane as the internal standard. Nuclear Overhauser effect (NOESY), homonuclear ($^1$H/$^1$H) correlation spectroscopy (COSY) and inverse gradient heteronuclear ($^1$H/$^{13}$C) correlation spectroscopy (HSQC and HMBC) were obtained using the standard Bruker pulse sequence for structural assignment of NMR spectra. Chemical shift values (δ) were given in ppm. Mass spectra and HRMS data were recorded on a Finnigan MAT 95 instrument for chemical ionisation (CI) and on a Varian MAT 711 instrument for electron impact ionisation (EI). The melting points were determined on an SMP 20 melting point apparatus (Büchi). Infrared spectra were obtained on a Bruker Vector 22 FT-IR spectrometer. Enantiomeric ratios were detected on a GC HRGC Mega 8560 (Fisons) or a GC HRGC 5300 (Carlo Erba Strumentazione). The exact conditions are reported in connection with each analyzed substance. Preparative HPLC was performed on a Shimadzu system with the following modules: DGU-20A5 Prominence Degasser, LC-20AT Prominence Liquid Chromatograph, SIL-20A Prominence Auto Sampler and a Kromasil 100 Si 5μm column (Knauer). The progress of the reactions was routinely monitored by GC analysis (HP 6890, capillary column HP-5, 80 °C initial temperature, heating rate 16 °C/min and final temperature 300 °C) or thin layer chromatography (TLC) on Silica gel 60 F254 (Merck) and the products were visualized with an ultraviolet lamp (254 and 365 nm) or an alcoholic anisaldehyde solution. Flash column chromatography was carried out on silica gel 60 (Fluka). All solvents were dried by standard methods and distilled before use. 2-Cyclopentenone 9a and 2-methyl-2-cyclopentenone 9b were purchased from Sigma Aldrich and were distilled before use.

The following compounds were prepared following literature procedures: trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene 2 (Danishefsky’s diene)$^{25}$; oxazaborolidinones 20a-c$^{26}$; Seebach’s titanium TADDOLate complex 23$^{21}$; chiral acyloxyborane complexes 24a-d$^{22}$; Nishida’s BINAMIDE complex 25$^{23}$.

For details of the synthesis of catalysts 21a-d, see supplementary information.

**General procedure for the Lewis acid-catalyzed Diels-Alder reaction of 2-cyclopentenones (9a), (9b) with Danishefsky’s diene (2)**

2-Cyclopentenone 9a (0.04 mL, 0.04 g, 0.48 mmol) was placed in a dry Schlenk flask and dissolved in 2 mL of CH$_2$Cl$_2$. 0.05 mmol of BF$_3$·Et$_2$O was added and the resulting mixture was stirred for 15 min. After cooling the reaction to the indicated temperature 0.12 mL (0.01 g, 0.58
mmol) trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (2) was added. After 5 min the end of reaction was detected using GC analysis. It was hydrolyzed with 2 mL 1N HCl and stirred heavily for 15 min at room temperature. The layers were separated and the aqueous layer was extracted with 3 x 3 mL of dichloromethane. Combined organic layers were washed with 5 mL of saturated NaHCO₃ solution, dried over MgSO₄ and the solvents were removed under reduced pressure.

**Cis-2,3,3a,4-Tetrahydro-1H-indene-1,5(7aH)-dione (10).** 2,3,3a,4-Tetrahydro-1H-indene-1,5(6H)-dione (12). After purification by flash chromatography (silica, eluant: 4:1 hexanes/iPrOH) a product mixture of the two double bond isomers 10 and 12 (43:57 ratio according to ¹H-NMR) was obtained, which could not be further separated. Yellow oil, yield 14.3 mg (20%), Rₜ = 0.3 (4:1 hexanes/iPrOH, UV).

**Isomer (10).** ¹H-NMR (500 MHz, CDCl₃): δ = 1.18 – 1.26 (m, 1H, 3-H₃a), 1.38 – 1.45 (m, 1H, 3-H₄), 1.57 – 1.64 (m, 1H, 2-H₃a), 1.69 – 1.77 (m, 1H, 2-H₄), 1.90 – 2.08 (m, 3H, 3a-H, 4-H), 2.29 – 2.33 (m, 1H, 7a-H), 5.84 (dd, J = 10.1 Hz, J = 2.6 Hz, 1H, 6-H), 6.24 (ddd, J = 10.1 Hz, J = 4.2 Hz, J = 0.7 Hz, 1H, 7-H) ppm. ¹³C-NMR (125 MHz, CDCl₃): δ = 24.6 (C-3), 32.9 (C-3a), 35.6 (C-2), 37.7 (C-4), 48.4 (C-7a), 128.9 (C-6), 141.4 (C-7), 194.4 (C-5), 211.5 (C-1) ppm.

**Isomer (12).** ¹H-NMR (500 MHz, CDCl₃): δ = 0.70 (ddddd, J = 20.5 Hz, J = 13.2 Hz, J = 10.9 Hz, 8.1 Hz, 1H, 3-H₃a), 1.47 (dd, J = 14.4 Hz, J = 12.0 Hz, 1H, 4-H₃a), 1.44 – 1.52 (m, 1H, 3-H₄), 1.69 – 1.77 (m, 2H, 2-H₃a, 6-H₃a), 1.90 – 2.08 (m, 1H, 2-H₄), 2.09 – 2.19 (m, 1H, 3a-H), 2.30 (dd J = 14.4 Hz, J = 5.4 Hz, 1H, 4-H₄), 2.39 (t, J = 3.7 Hz, 2H, 6-H₄), 6.33 (ddd, J = 3.7 Hz, J = 3.2 Hz, J = 0.7 Hz, 1H, 7-H) ppm. ¹³C-NMR (125 MHz, CDCl₃): δ = 26.6 (C-3), 35.9 (C-3a), 37.3 (C-2), 37.5 (C-6), 43.8 (C-4), 126.0 (C-7), 139.3 (C-7a), 200.8 (C-1), 204.3 (C-5) ppm. HRMS (EI): calcd. for C₁₀H₁₂O₂ 150.0681, found 150.0669 [M⁺]. MS (EI, 70 eV) m/z (%): 151.1 [M + H]⁺ (8), 150.1 [M⁺] (100), 122.1 (10), 109.1 (4), 108.1 (46), 107.1 [M⁺ – CH₂-C=O] (9), 95.1 (44), 94.1 (14), 80.1 (28), 79.0 (48), 66.1 (24), 55.0 (8), 39.0 (16). FT-IR (ATR): ν = 3426 (w), 2959 (m), 2367 (w), 2198 (w), 1975 (w), 1737 (s), 1714 (vs), 1676 (s), 1655 (vs), 1618 (m), 1456 (w), 1407 (m), 1386 (m), 1299 (w), 1245 (m), 1214 (s), 1182 (s), 1157 (s), 1108 (m), 1043 (m), 983 (m), 960 (m), 923 (w), 875 (m), 854 (m), 830 (m), 775 (m), 744 (m), 701 (w), 670 (w), 644 (w), 582 (w), 555 (w).

**Cis-2,3,3a,4-Tetrahydro-7a-methyl-1H-indene-1,5(7aH)-dione (18).** Brown oil, 78.7 mg (100%). ¹H-NMR (500 MHz, CDCl₃): δ = 0.85 (s, 3H, CH₃), 1.00 – 1.15 (m, 1H, 4.69 (m, 1.75 - 1.92 (m), and 2.00 – 2.20 (m) (7H, 2-H₂, 3-H₂, 3a-H, 4-H₂), 5.74 (dd, J = 10.1 Hz, J = 0.7 Hz, 1H, 6-H), 6.46 (dd, J = 10.1 Hz, J = 1.8 Hz, J = 0.7, 1H, 7-H) ppm. ¹³C-NMR (75 MHz, CDCl₃): δ = 21.4 (CH₃), 24.8 (C-3), 36.7 (C-3a), 37.0 (C-2), 41.5 (C-4), 51.1 (C-7a), 129.4 (C-6), 147.6 (C-7), 195.6 (C-5), 216.0 (C-1) ppm. HRMS (EI): calcd. for C₁₀H₁₃O₂ 164.0837, found 164.0840 [M⁺]. MS (EI, 70 eV) m/z (%): 164.1 [M⁺] (28), 109.1 [M⁺ – COCH₃] (100), 80.1 (32), 79.1 (56).

**Cis-Hexahydro-1H-inden-1,5(6H)-dione (13).** Compounds 10 and 12 (60.0 mg, 0.40 mmol) were placed in a dry Schlenk flask and dissolved in 4 mL of methanol. Triethylsilane (0.64 mL, 93.0 mg, 0.80 mmol) was added, followed by addition of 7.00 mg of PdCl₂ (4.00 μmol). The
mixture was stirred for 8 h at room temperature, then heated to 80 °C and stirred for 3 h under reflux. The residue was filtered off and the remaining organic layer was diluted with 5 mL of CH₂Cl₂. It was washed with 5 mL of each, H₂O and brine. The solvents were evaporated under reduced pressure. Red liquid, 20 mg (33%).¹

¹H-NMR (300 MHz, CDCl₃): δ = 1.71 – 1.81 (m, 1H, 3a-H), 1.94 – 2.54 (m, 10H, 2-H, 3-H, 7-H, 6-H, 4-H), 2.54 – 2.82 (m, 1H, 7a-H) ppm. ¹³C-NMR (75 MHz, CDCl₃): δ = 22.7, 26.4, 35.0, 37.4, 38.0, 42.9, 47.6 (C-2, C-3, C-3a, C-7a, C-7, C-6, C-4), 211.0 (C-5), 218.1 (C-1) ppm. Spectroscopic data were consistent with previously reported data for this compound.¹²

Ketalization of the double bond isomers (10, 12)

Compounds 10 and 12 (80.0 mg, 0.53 mmol), dissolved in 6 mL of benzene, were treated with 0.30 mL (0.33 g, 5.33 mmol) of ethylene glycol and 44.0 mg (0.18 mmol) of pyridinium p-toluenesulphonate. The solution was refluxed for 3 h. Another 0.30 mL (0.33 g, 5.33 mmol) of ethylene glycol and 44.0 mg (0.18 mmol) PPTS were added and the resulting solution was refluxed for further 60 min. The solvents were concentrated in vacuo. The residue was dissolved in 20 mL of diethyl ether and washed with 10 mL of each, saturated NaHCO₃ solution and brine and dried over MgSO₄. After purification by flash chromatography (2:1 hexanes/ethyl acetate) an inseparable mixture of monoketal 14 and diketal 15 (50:50 according to GC analysis) was obtained (75%).

cis-2′,3′,3a′,4′-Tetrahydrospiro[1,3-dioxolane-2,1′(1′H)-indenene]-5′(7a′H)-one (14). Rₜ = 0.3 (2:1 hexanes/ethyl acetate, UV). ¹H-NMR (300 MHz, C₆D₆): δ = 0.81 – 1.59 (m, 4H, 3-H, 3a-H, 7a′-H), 1.89 – 2.11 (m, 4H, 2-H, 4′-H), 2.94 – 3.25 (m, 6H, 1-H, 2-H, 7a-H, 5′-H), 5.76 (dd, J = 10.3 Hz, J = 2.3 Hz, 1 H, 6′-H), 6.18 (ddd, J = 10.3 Hz, J = 3.4 Hz, J = 0.9 Hz, 1H, 7′-H) ppm.

¹³C-NMR (75 MHz, CDCl₃): δ = 24.8, 28.7, 33.9, 39.1, 45.5 (C-2, C-3, C-3a, C-4, C-7a), 62.7, 63.6 (C-1, C-2), 116.8 (C-1), 129.5 (C-6), 143.8 (C-7), 195.9 (C-5). HRMS (ESI): calcd. for C₃₁H₄₅O₄Na 195.1021, found 195.1016 [M + Na]⁺. MS (EI) m/z: 217.1 [M + Na]⁺, 295.1 [M + H]⁺, 151.1, 133.1, 102.1. FT-IR (ATR): ν = 2927 (m), 2882 (m), 1720 (s), 1695 (s), 1605 (s), 1548 (s), 1430 (w), 1406 (m), 1320 (w), 1297 (w), 1244 (s), 1200 (w), 1103 (m), 1033 (m), 1021 (m), 950 (w), 833 (w), 802 (w), 759 (w), 688 (w), 645 (w), 577 (w), 497 (w).

cis-2′,3′,3a′,4′-Tetrahydrospiro[1,3-dioxolane-2,1′(1′H)-indenene-5′(7a′H),2″-1,3-dioxolane] (15). Rₜ = 0.5 (2:1 hexanes/ethyl acetate, UV). ¹H-NMR (300 MHz, C₆D₆): δ = 1.11 – 1.65 (m, 6H, 2′-H, 3′-H, 3′a-H, 4′-Hₐ), 1.81 (dd, J = 13.07 Hz, J = 9.9 Hz 1H, 4′-Hₐ), 2.48 – 2.58 (m, 1H, 7a′-H), 3.28 – 3.51 (m, 8H, H-1, H-2, H-1′, H-2′), 5.61 (ddd, J = 10.2 Hz, J = 1.6 Hz, J = 0.7 Hz, 1H, 7-H), 5.67 (dd, J = 10.2 Hz, J = 3.1 Hz, 1H, 6-H) ppm. ¹³C-NMR (75 MHz, CDCl₃): δ = 25.2, 32.2, 34.0, 35.7, 45.1 (C-2, C-3, C-3a, C-4, C-7a), 62.7, 63.0, 63.2, 63.6 (C-1, C-2, C-1′, C-2′), 104.5 (C-5), 116.4 (C-1), 129.0 (C-6), 133.3 (C-7). HRMS (ESI): calcd. for C₃₃H₅₉O₅Na⁺ 261.1103, found 261.1095. MS (ESI) m/z: 261.1 [M + Na]⁺, 239.1 [M + H]⁺, 219.1, 177.1, 133.1, 127.1. FT-IR (ATR): ν = 2927 (m), 2878 (m), 1697 (s), 1598 (s), 1536 (s), 1487 (w), 1452 (m), 1406 (m), 1334 (w), 1303 (w), 1228 (s), 1196 (w), 1124 (m), 1087 (m), 1055 (m), 1027 (m), 950 (w), 835 (w), 803 (w), 749 (w), 699 (w), 646 (w), 572 (w), 505 (w).
Synthesis of the hydrazones (16, 17)
2,4-Dinitrophenylhydrazine (0.52 g, 2.62 mmol) was dissolved in 2.50 mL concentrated H₂SO₄ and 3.75 mL of water were slowly added to this solution followed by addition of 12.5 mL ethanol. A solution of the two double bond isomers 10, 12 (78.0 mg, 0.52 mmol) in 5 mL of ethanol was then added. Immediately the precipitation of a red solid could be observed which was filtered off, washed with water and dried over P₂O₅ in vacuo. Using preparative HPLC (Kromasil; UV-detection; λmax = 356 nm; flow rate 10 mL/min; hexane/isopropyl alcohol 98:2) 2 mg of the bishydrazone 17 and 2 mg of the monohydrazone 16 could be obtained as red solids.

2,3,3a,4 -Tetrahydro-1H-indene-1,5(7aH)-dione 5-[2-(2,4-dinitrophenyl)hydrazono] (16).
Concerning the configuration of the C=N bond see ref. 13. Rf = 0.7 (1:1 hexanes/ethyl acetate, UV). ¹H-NMR (300 MHz, CDCl₃): δ = 1.78 – 1.90 (m), 2.34 – 2.48 (m), 2.56 – 2.86 (m) 2.87 – 3.21 (8H, 2-H, 3-H, 3a-H, 7a-H, 4-H), 6.12 (ddd, J = 10.0 Hz, J = 3.9 Hz, J = 0.7 Hz, 1H, 7-H), 6.46 (dd, J = 10.0 Hz, J = 2.7 Hz, 1H, 6-H), 8.01 (d, J = 9.5 Hz, 1H, 2'-H), 8.29 – 8.37 (m, 1H, 3'-H), 9.09 – 9.17 (m, 1H, 5'-H), 11.31 (br, 1H, NH) ppm. ¹³C-NMR (75 MHz, CDCl₃): δ = 25.6 (C-3), 26.8 (C-3a), 33.1 (C-2), 37.4 (C-4), 50.0 (C-7a), 112.4, 116.3, 116.7, 128.4, 131.1, 144.6 (Ar), 123.4 (C-6), 130.1 (C-7), 150.3 (C-5), 215.4 (C-1) ppm. HRMS (ESI): calcd. for C₁₅H₁₄N₈O₄Na⁺ 535.0862, found 535.0864. MS (ESI) m/z: 353.1 [M + Na]⁺, 331.1 [M + H]⁺, 304.3, 276.2. FT-IR (ATR): ν = 3311 (w), 3102 (w), 2925 (w), 2358 (w), 2155 (m), 1716, 1610 (s), 1588 (s), 1501 (s), 1422 (m), 1327 (s), 1309 (s), 1223 (m), 1134 (m), 1088 (s), 922 (w), 833 (m), 798 (m).

2,3,3a,4 -Tetrahydro-1H-indene-1,5(7aH)-dione 1,5-bis[2-(2,4-dinitrophenyl)hydrazono] (17).
Concerning the configuration of the C=N bond see ref. 13. Rf = 0.9 (1:1 hexanes/ethyl acetate, UV). ¹H-NMR (500 MHz, CDCl₃): δ = 0.75 – 0.99 (m), 1.16 – 1.40 (m), 1.83 – 2.95 (m) (8H, 2-H, 3-H, 3a-H, 7a-H, 4-H), 6.23 (ddd, J = 10.1 Hz, J = 3.6 Hz, J = 0.6 Hz, 1H, 7-H), 6.46 (dd, J = 10.1 Hz, J = 2.5 Hz, 1H, 6-H), 7.96 – 8.03 (m, 2H, 2'-H, 2'-H), 8.35 (m, 2H, 3'-H, 3'-H), 9.15 (m, 2H, 5'-H, 5'-H), 10.87, 11.32 (s, 2H, NH) ppm. ¹³C-NMR (125 MHz, CDCl₃): δ = 25.2 (C-3), 26.9 (C-3a), 29.6 (C-2), 34.8 (C-4), 44.8 (C-7a), 112.4, 116.3, 116.7, 127.7, 130.12, 134.3 (Ar), 123.50 (C-6), 130.17 (C-7), 165.4 (C-5), 173.0 (C-1) ppm. HRMS (APCI): calcd. for C₂₁H₁₈N₈O₈ 511.1326, found 511.1315 [M + H]⁺. MS (APCI) m/z: 511.1 [M + H]⁺, 491.1, 477.1, 413.1, 342.1, 328.1, 294.1, 279.1. FT-IR (ATR): ν = 3310 (w), 3102 (w), 2925 (w), 2925 (w), 2050 (w), 1981 (w), 1614 (s), 1589 (s), 1502 (s), 1420 (m), 1332 (s), 1310 (s), 1220 (m), 1080 (m), 973 (w), 921 (m), 832 (m), 762 (w), 742 (m), 717 (w), 686 (w), 639 (w), 568 (w).

General procedure for the preparation and use of chiral Diels-Alder catalysts (20a-c) and (21a-d)
A two necked, round bottom flask, equipped with a pressure-equalizing addition funnel (containing a cotton plug and ca. 10 g of 4Å molecular sieves) was charged with (S)-α,α-diphenyl-2-pyrolidinemethanol 21a (0.94 g, 3.71 mmol), tri-α-tolylboroxine (0.36 g, 1.01 mmol) and 35 mL of toluene. The resulting solution was heated to reflux. After 3 h toluene was directly distilled off using a Claisen bridge. This distillation protocol was repeated three times by
recharging with 3 x 30 mL of toluene. The following concentration in vacuo (0.1 mmHg, 1 h) afforded the corresponding oxazaborolidine as clear oil which was then dissolved in CH₂Cl₂ and used in Diels-Alder experiments.

To an aliquot of the oxazaborolidine precursor (0.07 mmol, theoretical) in 5 mL of CH₂Cl₂ at -78 °C was added triflic acid (0.2 M solution in CH₂Cl₂, freshly prepared, 300 μL, 0.06 mmol) dropwise. During the addition, the catalyst solution turned orange in color, but cleared up instantaneously. Near the end, a small amount of orange precipitate was observed. After 10 to 15 min at -78 °C, the orange precipitate disappeared and a yellow homogeneous solution was obtained. In the following 0.07 mL (0.07 g, 0.70 mmol) of 2-methyl-2-cyclopentenone 9b was added and the reaction was stirred for further 15 min. Danishefsky’s diene 2 (0.16 mL, 0.14 g, 0.84 mmol) was added and at the end of reaction, detected using GC analysis, it was hydrolyzed with 2 mL 1N HCl and stirred heavily for 15 min at room temperature. The layers were separated and the aqueous layer was extracted with 3 x 3 mL of CH₂Cl₂. Combined organic layers were washed with 5 mL of saturated NaHCO₃ solution, dried over MgSO₄ and the solvents were removed under reduced pressure.

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References


8. The formation of 1,3,5-triacetylbenzene can be explained with the cyclization reaction of 4-methoxy-3-butenone - derived from Danishefsky’s diene - in acidic medium. See also: Kumbaraci, V.; Ergunes, D.; Midilli, M.; Begen, S.; Talinli, N. J. Heterocyclic Chem. 2009, 46, 226.


11. See supplementary information for a detailed discussion of the NMR data.


13. The NMR spectra of compounds 16, 17 did not show any evidence for E/Z mixture. However in agreement with literature precedence the configuration was arbitrarily assigned. See: (a) Yusubov, M. S.; Chi, K.-W.; Park, J. Y.; Karimov, R.; Zhdankin, V. V. Tetrahedron Lett. 2006, 47, 6305. (b) Ramirez, F.; Kirby A. F. J. Am. Chem. Soc. 1952, 74, 4331.


15. For details of the isolation of the pure monoketal 14 and diketal 15, see supplementary information.


