Asymmetric Synthesis of β-Substituted α-Methylenebutyrolactones via TRIP-Catalyzed Allylation: Mechanistic Studies and Application to the Synthesis of (S)-(−)-Hydroxymatairesinol

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Abstract: Asymmetric allylation of (hetero)aromatic aldehydes by a zinc(II)-allylbutyrolactone species catalyzed by a chiral BINOL-type phosphoric acid gave β-substituted α-methylenebutyrolactones in 68 to >99% ee and 52–91% isolated yield. DFT studies on the intermediate Zn2+ complex – crucial for chiral induction – suggest a six-membered ring intermediate, which allows the phosphoric acid moiety to activate the aldehyde. The methodology was applied to the synthesis of the antitumour natural product (S)-(−)-hydroxymatairesinol.

Keywords: asymmetric allylation; butyrolactones; chiral phosphoric acids; hydroxymatairesinol; organozinc reagents

Asymmetric allylation is a key transformation in organic synthesis, which has been enabled through addition of various organometallic species onto aldehydes and ketones forming up to two chiral centers in a single step. A variety of methodologies has been developed, mainly using allylboronates or silanes in combination with stoichiometric or catalytic amounts of the chiral reagent or mediator.[1] However, the asymmetric synthesis of butyrolactone-based natural products (e.g., lignans) via allylation of aldehydes still remains troublesome,[2] although racemic methods have been recently developed.[3] Only a few catalytic approaches exist.[4] Allylboronates have proven to be a unique tool for asymmetric allylation, but the preparation of lactono-based allylboronates – required for the preparation of the title compound class – is unknown. Allyl-Sn and allyl-Si esters, another widely used class of allylating reagents, require additional Lewis acid activation during the allylation step,[5] which can harm the lactone scaffold. Therefore, new methodologies are desirable, whereby stereoselectivity is induced through reactants which show a broad functional group tolerance including esters and lactones. For racemic allylation variants, organozinc compounds are regularly used, because they are easily prepared from the corresponding allylic halides and zinc dust[6] and show a high tolerance towards a variety of functional groups.[7] To date, reports on the asymmetric Zn2+-mediated Barbier-type allylation reaction are scarce,[8] although high diastereoselectivity can be induced regarding the syn/anti ratio of the two chiral centers formed during the allylation with butyrolactone 4 (Scheme 1).[9] A possible explanation for the lack of asymmetric protocols may be that most reactions are run in highly coordinating and/or polar solvents (such as THF, DMF, DME or even water) which is essential for metal insertion into the carbon-halide bond. On the other hand, polar media enhance the reaction rate of the uncatalyzed (achiral) reaction by impeding the coordination of chiral additives and thus interfere with chirality transfer. However, catalytic methods involving chiral zinc catalysts have been reported recently,[9] demonstrating that chiral induction by organozinc compounds is possible.

Our study was initiated by the identification of an appropriate catalyst for our model reaction, using aldehyde 2, which serves as precursor for (S)-(−)-hy-
Chiral phosphoric acids have emerged as a new class of organocatalysts since the pioneering work of Akiyama[10] and Terada[11] and their tremendous potential as chiral reagents has sparked many investigations.[12] In this context, Antilla and Jain have recently applied chiral phosphoric acids, such as 3,3'-bis(2,4,6-trisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (TRIP),[13] to the asymmetric allylboration of aldehydes with high stereoselectivities for C–C bond formation.[14] Although mechanistic proposals for phosphoric acid catalysis involving aldehydes are rare, we identified (S)-TRIP as being a potential catalyst candidate since initial experiments indicated that reasonable amounts of product with promising levels of enantiomeric excess (ee > 20%, syn:anti 9:91) are formed in toluene/THF at a catalyst loading of 5 mol% (Table 1, entry 1). The addition of NH4Cl for

Table 1. Optimization of asymmetric allylation.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>R =</th>
<th>Conversion [%][b]</th>
<th>syn:anti[c]</th>
<th>ee [%][d]</th>
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<tbody>
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<td>toluene/THF 1/1</td>
<td>H</td>
<td>76</td>
<td>9:91</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>toluene/EtOH 1/1</td>
<td>H</td>
<td>90</td>
<td>8:92</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>toluene/1-decanol 1/1</td>
<td>H</td>
<td>41</td>
<td>12:88</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>toluene/NMP 1/1</td>
<td>H</td>
<td>67</td>
<td>4:96</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>toluene/DME 1/1</td>
<td>H</td>
<td>&gt; 99</td>
<td>5:95</td>
<td>&lt;1</td>
</tr>
<tr>
<td>6</td>
<td>toluene/DME 99.5/0.5</td>
<td>H</td>
<td>8</td>
<td>10:90</td>
<td>75</td>
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<tr>
<td>7</td>
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<td>22</td>
<td>&lt;1; &gt; 99</td>
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<td>8</td>
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<td>H</td>
<td>40</td>
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<td>17</td>
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<tr>
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<td>72</td>
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<td>3:97</td>
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<td>&lt;1; &gt; 99</td>
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</table>

[a] Reaction conditions: aldehyde 2 (entries 1–15) or 5 (entries 16–19, 40 mM), bromolactone 4 (1.5 equiv.), Zn dust (1.75 equiv.), NH4Cl (3.5 equiv.), 4°C, 720 rpm, 16 h.
[b] Conversions were determined via HPLC-UV at 215 nm.
[c] The syn:anti ratios were determined via HPLC-UV analysis.
[d] The ees were determined via HPLC-UV analysis on a chiral stationary phase.
[e] 50 mol% of (S)-TRIP.
[f] 10 mol% of (S)-TRIP and 4 equiv. of NH4Cl.
[g] 10 mol% of (S)-TRIP, 8 equiv. of NH4Cl and 2 equiv. of 4.
[h] Experiment was conducted at –30°C.
[i] 20 mol% of (S)-TRIP, 8 equiv. of NH4Cl and 2 equiv. of 4.

Scheme 1. Model reaction for optimization of the asymmetric allylation.

MeO
RO
H
(R)-TRIP (5 mol%), Zn, NH4Cl, solvent,
4°C, 16 h
MeO
RO
OH
HO
OMe
MeO
HO
OH
HO
acidic activation of the Zn surface in allylation reactions[3] was essential; no product formation was observed in its absence. Noteworthy, activation according to Knochel et al. (TMSCl + 1,2-dibromoethane)[16] showed positive effects on the conversion, but gave racemic product. Upon addition of the potassium salt of the chiral phosphoric acid we observed declining conversion and enantioselectivity (66% conversion and 10% ee, compare with Table 1, entry 1). Changing the inserting metal to indium slowed down the uncatalyzed reaction. However, no chiral induction was found upon addition of the chiral phosphoric acid. Experiments using the preformed phosphoric acid salt (TRIP/C0
\text{NH}_4^+) showed reduced conversions and stereoselectivities. Alternatively, the Zn$^{2+}$-TRIP species (acting as a catalytically active Lewis acid) would lead to a transition state intermediate via single coordination with a long distance between the chirality-inducing (i-Pr)$_2$C$_6$H$_2$ ligands and the lactone moiety, which could not explain the high (dia)stereoinduction experimentally observed[20a] (see Figures S01 and S02 in the Supporting Information).

In summary, these observations lead us to the conclusion that the catalytically active species would be the protonated phosphoric acid, coordinating the zinc core via the P=O moiety (Figure 1). Since acceleration of the same reaction by Brønsted acids has been previously observed, we assume that the aldehyde is activated via the acidic P=O[3a].

Since the reaction medium was expected to be an important parameter, careful optimization studies, especially of the polar component, were conducted. The most important results are summarized in Table 1 (for detailed information see the Supporting Information): Compared to the initial results with toluene/THF, ethanol gave high yields but only racemic product (entry 2). An extension of the alkane chain (1-decanol) showed improved selectivity in combination with a decreased conversion, implying that either steric issues in the coordination of the transition state intermediate or the dipole moment of the solvent were important for the stereoselectivity (entry 3). Solvents with higher coordination strength/dipole, such as NMP (N-methylpyrrolidone) and DME (1,2-dime-
thoxyethane) completely destroyed the chiral induction due to impeded ligand exchange on the zinc metal core (entries 4 and 5). However, at reduced levels of DME (0.5%), elevated ees were observed again going in hand with diminished activity (entry 6). Non-coordinating ethers, such as MTBE (methyl tert-butyl ether) gave high selectivities, but low conversions (entry 7). In pure MTBE the ee was decreased without an increase in conversion. Dichloromethane proved to be an attractive alternative to toluene, as conversion was almost doubled with a slight decline in stereocontrol (entries 8 and 13). Since diethyl ether had emerged as a potential polar candidate, similar ethers were tested. Based on their steric properties it became clear that the inner coordination sphere of the zinc center seemed to have the highest influence, as ethers with higher steric hindrance had a positive influence on the stereoinduction rather than the alkyl chain length (entries 8–12). Further increase in selectivity was achieved when toluene was added again and these ternary solvent mixtures gave the first ee activity was achieved when toluene was added again and these ternary solvent mixtures gave the first ee activity was achieved when toluene was added again and these ternary solvent mixtures gave the first ee activity was achieved when toluene was added again and these ternary solvent mixtures gave the first ee activity was achieved when toluene was added again and these ternary solvent mixtures gave the first ee activity was achieved when toluene was added again and these ternary solvent mixtures gave the first ee activity was achieved when toluene was added again and these ternary solvent mixtures gave the first ee. Benzyl-protected vanilline was opposite to that of the allylboration with the same catalyst\textsuperscript{[14]} owing to the different mechanism of the latter reaction, which requires acidic activation of the boronic ester.\textsuperscript{[20]} Based on the experimental results (anti-configured products) and the considerations on the catalyst’s nature (protonated phosphoric acid coordinated to zinc) DFT calculations yielded only model structure \textbf{15} as energetically and mechanistically reasonable intermediate (Figure 1), when stationary points were investigated using the M06 functional with a triple-\textgamma{} basis set (6-311G\textsuperscript{**}).\textsuperscript{[22]} The structure \textbf{15} consists of a double coordination of the P(O)OH group to the zinc-allyl-aldehyde ring system in a chair-like transition state (Zimmerman–Traxler model). Both six-membered rings are distorted and zinc coordinates the allylic carbon atom. However, the distance to the adjacent C atom is in the order of 2.4 to 2.8 Å, forecasting the C–C bond to be formed and causing a significant ring contraction. The phosphoric acid coordinates the Zn center through the P=O moiety, while the P–OH unit activates the phosgene giving a flat six-membered ring (coordination of the phosphoric acid yields >200 kcal mol\textsuperscript{−1}).\textsuperscript{[23]} With this concept about the intermediate's geometry, we then focused on the mode of chiral induction during alcohol formation by investigating two stereochemical situations: \textit{S}_{\textit{aal}}S_{\textit{alc}}R and \textit{S}_{\textit{aal}}R_{\textit{alc}}S.\textsuperscript{[23]} The combination \textit{S}_{\textit{aal}} and \textit{R}_{\textit{alc}}\textit{S} was favoured by 1.7 kcal mol\textsuperscript{−1}, which translates to an ee of 91% (experimentally observed 94%). Careful analysis of the calculated structures (Figure 1) did not reveal any significant steric hindrance between the phenyl substituent of the substrate and the catalyst in both isomeric structures.
However, steric repulsion can be found between the isopropyl moieties of the ligand and the lactone (4.6 vs. 3.2 Å), which results in shorter Zn-allyl-carbon distances in the favoured $S_{ax}R_{alc}$ structure (2.4 vs. 2.6 Å; Figure 1).

In order to comprise contributions from non-catalyzed turnovers, stabilization of the proposed intermediate by coordination of different ethers [Me$_2$O, Et$_2$O, (i-Pr)$_2$O and THF] was assessed by means of continuum models (IEF-PCM). Overall, stabilization by a single solvent molecule lies within the range of ca. –13 to –15 kcal mol$^{-1}$, with a minimum energy for THF (for details see the Supporting Information). Therefore, an acceleration of the non-catalyzed reac-

<table>
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<tr>
<th>Entry</th>
<th>Product</th>
<th>Conversion [%]$^b$</th>
<th>syn:anti$^c$</th>
<th>ee [%]$^d$</th>
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<td>94</td>
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</tr>
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<td>&gt;99 (91)</td>
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<td>n.d.$^g$</td>
</tr>
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<td>5$^f$</td>
<td><img src="Product5.png" alt="Product Image" /></td>
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<td>96</td>
</tr>
<tr>
<td>6$^i$</td>
<td><img src="Product6.png" alt="Product Image" /></td>
<td>88$^i$</td>
<td>&lt;1:1 &gt;99</td>
<td>97</td>
</tr>
<tr>
<td>7$^j$</td>
<td><img src="Product7.png" alt="Product Image" /></td>
<td>95 (91)</td>
<td>&lt;1:1 &gt;99</td>
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<tr>
<td>8$^k$</td>
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<td>86 (80)</td>
<td>&lt;1:1 &gt;99</td>
<td>97</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: aldehyde (20 mM), bromolactone 4 (1.1 equiv.) Zn dust (6 equiv.), NH$_4$Cl (8 equiv.), toluene/(i-Pr)$_2$O 4/1, 4°C, 720 rpm, 16 h.

$^b$ Conversions were determined via HPLC-UV at 215 nm, isolated yields are given in brackets.

$^c$ The syn:anti ratio was determined via $^1$H NMR.

$^d$ The ee was determined via HPLC-UV analysis on a chiral stationary phase.

$^e$ 2 equiv. of 4 were used.

$^f$ (R)-TRIP (20 mol%) gave 6.

$^g$ Not determined due to inseparable syn:anti-mixture.

$^h$ No isolated yields are given due to inseparable minor impurities (for details see Supporting Information).
tion by higher coordinating ethers can be deduced, explaining the reduced ee value in presence of these solvents.

In conclusion, the catalytic asymmetric allylation of aldehydes by allylzinc species using a chiral, BINOL-derived phosphoric acid (TRIP) was demonstrated. Careful choice of the reaction conditions gave high isolated yields and almost perfect enantio- and diastereoselectivities. The preparative scale applicability of the method was demonstrated by the total synthesis of (S)-(--)-hydroxymatairesinol (1) in 98% ee and 46% overall yield, starting from aldehyde 5 (including its benzyl protection). Finally, a proposal for the transient species was developed by DFT calculations, which explains the stereochemical outcome due to steric interaction of the lactone residue with the ligand of the TRIP-catalyst.

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References

Asymmetric Synthesis of $\beta$-Substituted $\alpha$-Methylenebutyrolactones via TRIP-Catalyzed Allylation

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[22] The splitting into the two parts results in two charged subunits, which probably leads to overestimated stabilization energies due to the lack of dissipation of charge in the surroundings. However, the high energy indicates that the uncoordinated species is significantly less stable.

[23] $S_{\text{ax}}R_{\text{ax}}S$ refers to: $S_{\text{ax}}$ = axial chirality of catalyst is ($S$); $R_{\text{ax}}$ = alcohol is ($R$)-configured, $S$ = configuration at the chiral center formed in the lactone ring.

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