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Catalytic Enantioselective Synthesis of Prostaglandin
E₁ Methyl Ester Using a Tandem 1,4-Addition–Aldol Reaction to a Cyclopenten-3,5-dione Monoacetal

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Conjugate addition reactions are among the most important carbon-carbon bond formation reactions in organic synthesis,¹ and considerable progress has been made in the development of asymmetric Michael additions and 1,4-additions of organometallic reagents.² Recently, highly enantioselective copper-catalyzed conjugate addition reactions of diorganozinc reagents to enones have been reported.³ Among the various chiral ligands introduced for this purpose phosphoramidite ⁴, developed in our laboratories, shows nearly complete stereocontrol in the reaction of (function-alized) dialkylzinc (R₂Zn) reagents with six-, seven- and eight-membered cycloalkenones.⁵ On the basis of this methodology, catalytic routes are now available to enantiomerically pure products, embedding cyclohexane and larger rings in their structure.⁶ In contrast, the catalytic enantioselective 1,4-addition to 2-cyclopentenone is a major challenge, particularly because chiral cyclopentane structures are ubiquitous in natural products. Employing TADDO-L-based phosphoramidite ligands we obtained up to 62% ee when the Et₂Zn addition to 2-cyclopentenone was run in the presence of molecular sieves.⁷ Furthermore, with using chiral bidentate phosphoramidite ligands, the enantioselectivity improved to 83%.⁸ Chan⁹ reached 89% ee using a diphosphite ligand, whereas Pfaltz¹⁰ enhanced the enantioselectivity in this addition to 94%. Recently Hoveyda¹¹ reported ee values up to 97% using a chiral peptide-based phosphine ligand in the 1,4-addition of diethylzinc to 2-cyclopentenone. Although these catalysts give excellent enantioselectivities, the isolated yields for the 3-substituted cyclopentanones are often moderate. Possible reasons are the lower reactivity of 2-cyclopentenone in comparison with other cyclic enones, the side-reactions of the resulting zinc enolate with the starting material and the high volatility of the 1,4-addition product. Performing the reaction in the presence of an acetaldehyde increases the yield considerably.¹²

We report here the highly enantioselective catalytic tandem 1,4-addition–aldol reaction of dialkylzinc reagents to cyclopenten-3,5-dione monoacetals in the presence of aldehydes. These compounds show a higher reactivity, and the heavily function-alized products are less volatile. The usefulness of this new method is illustrated by the total synthesis of (S)-(+-)PGF₁₇ methyl ester in seven steps using achiral starting materials and only a catalytic amount of a chiral copper complex.

Monoacetals 1a and 1b were employed in the tandem 1,4-addition–aldol reaction with various aldehydes and dialkylzinc reagents (Scheme 1).¹² The catalyst was prepared in situ from 2 mol % Cu(OTf)₂ and 4 mol % (S.R)-phosphoramidite. Full conversion was reached after 16 h to provide exclusively trans substituted cyclopentanones 2a-f in isolated yields up to 76% (Table 1). Excellent stereocontrol is also observed in the subsequent aldol step, as for the hydroxy ketones 2a-f diastereomeric ratios higher than 95:5 were measured. The configuration of the main product was determined by NOESY-NMR. The adducts 2a-f were converted into the corresponding diketones 3a-f in good yields to give single diastereomers suitable for ee determination by chiral HPLC. The enantioselectivity strongly depends on the acetal moiety present in the starting material as 87% ee for enone 3a (entry 1) and 94% ee for enone 3c (entry 3) was obtained. The use of different dialkylzinc reagents, however, has no influence on the selectivity of this reaction (entries 3 and 4). The structure of the aldehyde has a minor influence: the use of benzaldehyde and p-bromo benzaldehyde shows ee values of 94% and 97%, respectively (entries 4 and 6).

We have demonstrated therefore, that in the presence of 2 mol % of (S,R)-4-Cu(OTf)₂ nearly complete stereocontrol over the formation of three consecutive stereocenters in this tandem 1,4-addition–aldol reaction is achieved, providing multifunctional cyclopentanones. These results inspired us to demonstrate the

(12) (a) Yoshida, Z.; Kimura, M.; Yoneda, S. Tetrahedron Lett. 1995, 36, 2839. (b) All compounds exhibited spectroscopic data (¹H NMR, ¹³C NMR, HRMS) in accordance with the structures. Details of the synthesis of 1a, 1b, and 5 will be published in due course.

Scheme 1

Table 1. Results of Tandem 1,4-Addition–Aldol Reactions According to Scheme 1

<table>
<thead>
<tr>
<th>entry</th>
<th>enone</th>
<th>R 2Zn</th>
<th>R’CHO</th>
<th>yield [%]¹</th>
<th>ee (3a-f) [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Et</td>
<td>Ph</td>
<td>2a</td>
<td>67 87</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>n-Bu</td>
<td>Ph</td>
<td>2b</td>
<td>64 87</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>Et</td>
<td>Ph</td>
<td>2c</td>
<td>76 94</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>n-Bu</td>
<td>Ph</td>
<td>2d</td>
<td>69 94</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>Et</td>
<td>p-Bri-Ph</td>
<td>2e</td>
<td>69 96</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td>n-Bu</td>
<td>p-Bri-Ph</td>
<td>2f</td>
<td>64 97</td>
</tr>
</tbody>
</table>

¹ Isolated Yields. ² Determined with HPLC (Daicel CHIRAL PAK-AD).
of 7 proceeds with 95% stereoselectivity using Zn[BH$_4$]$_2$ in ether at -30 °C. Compound 8 was isolated after chromatography as a single isomer in 63% yield with an ee of 94%. In the next step the silyl substituent was removed using Bu$_4$NF in THF/DMSO to give compound 9 (Scheme 3). This concept comprises a novel protection and deprotection sequence for enones suitable for the catalytic 1,4-addition with dialkylzincs. The cleavage of vinyl carbon-silicon bonds with Bu$_4$NF was developed by Nozaki. However, under the normal reaction conditions hydrolysis of compound 9 was observed to be caused by water in the commercial THF solution of Bu$_4$NF. Adding first sacrificial methylpropionate to remove the water by hydrolysis and only afterwards 8, the desilylated compound 9 was obtained as the only product and used without further purification. Acetylation of 9 afforded 10 in 71% yield over two steps.

The 1,3-allylic transposition of 10 with a catalytic amount of Pd(CH$_3$CN)$_2$Cl$_2$ in THF proceeded with reasonable yield and full retention of configuration to give allylic acetate 11 with the required stereochemistry. After deacetylation in the presence of K$_2$CO$_3$ in MeOH, compound 12 was obtained in excellent yield. The last step is the deprotection of the ketone functionality to provide the labile $\beta$-hydroxy ketone moiety of the prostaglandin. This conversion was realized using a catalytic amount of (NH$_4$)$_2$Ce(NO$_3$)$_6$ under nearly neutral conditions. In this way PGE$_1$ methyl ester is obtained in 7% overall yield with 94% optical purity in seven steps from 1b.

In conclusion we have demonstrated that cyclopenten-3,5-dione monoacetics give highly enantioselective tandem 1,4-addition-aldol reactions in the presence of dialkylzinc reagents and aldehydes using a catalytic amount of Cu(OTf)$_2$ and phosphoramidite ligand 4. Furthermore this reaction is the key step in a short total synthesis of PGE$_1$ methyl ester, comprising a new route to this natural product.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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21. The analytical and spectral data (TLC, HPLC, $^1$H NMR, $^{13}$C NMR, CD, MS) of 12 were identical with those of authentic material (Sigma) with $\delta_{H}$ $^1$-51 ppm for 1.0, CH$_3$OH of 13 were identical with those of authentic material (Sigma) with $\delta_{C}$ $^1$-54 ppm for 1.0, CH$_3$OH.